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60/233,180 15 September 2000 (15.09.2000) US
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
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(54) Title: ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING CODON OPTIMIZED HIV-1 GAG, POL, NEF AND MODIFICATIONS

(57) Abstract: First generation adenoviral vectors and associated recombinant adenovirus-based HIV vaccines which show enhanced stability and growth properties and greater cellular-mediated immunity are described within this specification. These adenoviral vectors are utilized to generate and produce through cell culture various adenoviral-based HIV-1 vaccines which contain HIV-1 gag, HIV-1 pol and/or HIV-1 nef polynucleotide pharmaceutical products, and biologically relevant modifications thereof. These adenovirus vaccines, when directly introduced into living vertebrate tissue, preferably a mammalian host such as a human or a non-human mammal of commercial or domestic veterinary importance, express the HIV-1 Gag, Pol and/or Nef protein or biologically modification thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding HIV-1 Gag, encoding codon optimized HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease, reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The adenoviral vaccines of the present invention, when administered alone or in a combined modality regime, will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C12N 15/86

US CL : 435/456

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/205.1, 207.1, 227.1, 233.1; 435/69.1, 69.3, 173.3, 235.1, 320.1, 456; 530/23.72;

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
Please See Continuation Sheet

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 96/39178 (ERTL et al.) 12 December 1996 (12.12.1996), see page 5, 6,10, 12, 13 and claims 1 and 5.	1-3, 8-11, 18 ----- 4, 5, 13-17, 29, 30, 32, 34, 35, 37
X --- Y	US 6,019,978 A (ERTL et al.) 1 February 2000 (01/02/2000), see columns 2, 7 and 8.	1-3, 8-11, 18 ----- 4, 5, 13-17, 29, 30, 32, 34, 35, 37
X,P	US 6,287,571 A A (ERTL et al.) 11 September 2001 (11/09/2001), see columns 2, 7, 8 and claim 1.	1, 9, 18
X --- Y	US 5,643,579A (HUNG et al.) 1 July 1997 (01/07/1997), see examples 1, 2, 25 and 26.	1-3, 8, 9-11, 18 ----- 4,5,13-17, 29, 30, 32, 34, 35, 37
Y	WANG et al. The use of an E1-deleted, replication -defective adenovirus recombinant expressing the rabies virus glycoprotein for early vaccination of mice against rabies virus. Journal of Virology (March 1997) Vol. 71, No. 5, pp 3677-3683.	1-3, 9-11, 13-18



Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z" document member of the same patent family

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## C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NATUK et al. Immunogenicity of recombinant human adenovirus -human immunodeficiency virus vaccines in chimpanzees. Aids Research and Human Retroviruses (1993) Vol. 9, No. 5, pp395-404, see material and methods.	1, 9, 29, 30, 32
Y	PREVEC et al. Immune response to HIV-1 gag antigens induced by recombinant adenovirus vectors in mice and rhesus macaque monkeys. Journal of Acquired Immune Deficiency Syndrome. (1991) Vol. 4, No. 6 pp. 568-76, see abstract.	1, 9, 29, 30, 32
Y	LORI et al. Rapid protection against human immunodeficiency virus type 1 (HIV-1) replication mediated by high efficiency non-retroviral delivery of genes interfering with HIV-1 tat and gag. Gene Therapy (1994) Vol. 1, No. 1, pp. 27-31, see abstract.	1, 9
Y	PFARR et al. Differential effects of polyadenylation regions on gene expression in mammalian cells. DNA (1986) Vol. 5, No. 2, pp. 115-22, see abstract.	16
Y	NATUK et al. Adenovirus vectored vaccine. Developmental Biological Standards (1994) Vol. 82, pp. 71-77, see abstract.	1, 9

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## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claim Nos.: 31  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
This claim could not be searched because applicant did not provide a CRF.
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-5, 8-11, 13-18, 29-32, 34, 35, 37

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

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The special technical feature of group 4, 16 and 31 is considered to be a method of producing recombinant adenoviral particles. Each group contains different sequences hence the resulting particles would have different structures and functions associated with the particle.

The special technical feature of group 5, 17 and 32 is considered to be a method of producing a cellular mediated immune response to the heterologous protein encoded by the different adenoviral vectors. Each group contains different sequences encoding different protein, therefore the resulting immune response will also be different.

The special technical feature of group 6, 18 and 33 is considered to be a method of producing a cellular mediated immune response to the heterologous protein encoded by the different adenoviral vectors in conjunction with immunizing the individual a DNA plasmid vaccine. Each method contains different sequences encoding a different protein, therefore the resulting immune response will also be different.

Accordingly, groups 1-48 are not so linked by the same or corresponding technical feature as to form a single general inventive concept.

### Continuation of B. FIELDS SEARCHED Item 3:

WEST 2.0, STN-BIOSIS, MEDLINE

adenoviral vector, deletion, HIV, Gag, polyadenylation signal, CMV promoter

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		and <u>ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 1)</u> inserted in <u>E1</u> .
14	55	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> and <u>ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 5)</u> inserted in <u>E1</u> .
15	55	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> and <u>ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Pol protein (SEQ ID NO: 7)</u> inserted in <u>E1</u> .
16	57-61	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Pol protein.
17	62, 65, 66	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle.
18	63, 64	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle in addition to administering a DNA plasmid vaccine.
19	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 9)</u> inserted in the parallel orientation of <u>E1</u> .
20	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 11)</u> inserted in the parallel orientation of <u>E1</u> .
21	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 13)</u> inserted in the parallel orientation of <u>E1</u> .
22	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 15)</u> inserted in the parallel orientation of <u>E1</u> .
23	71	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 9)</u> inserted in the antiparallel orientation of <u>E1</u> .
24	71	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 11)</u> inserted in the antiparallel orientation of <u>E1</u> .
25	71	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 13)</u> inserted in the antiparallel orientation of <u>E1</u> .
26	71	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 15)</u> inserted in the antiparallel orientation of <u>E1</u> .
27	74	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> and <u>ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 9)</u> inserted in <u>E1</u> .
28	74	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> and <u>ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an <u>HIV Nef protein (SEQ ID NO: 11)</u> inserted in <u>E1</u> .
29	74	The claim is directed to an adenoviral vector that is at least partially deleted of <u>ΔE1</u> and <u>ΔE3</u> , the vector contains the cis-acting packaging sequence of the wild type

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		and $\Delta E3$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 1) inserted in E1.
14	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 5) inserted in E1.
15	55	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Pol protein (SEQ ID NO: 7) inserted in E1.
16	57-61	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Pol protein.
17	62, 65, 66	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle.
18	63, 64	The claim is directed to a method of generating a cellular mediated immune response to HIV Pol protein with the recombinant adenoviral particle in addition to administering a DNA plasmid vaccine.
19	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in the parallel orientation of E1.
20	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in the parallel orientation of E1.
21	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in the parallel orientation of E1.
22	67-70, 72, 73, 75	The claims are directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in the parallel orientation of E1.
23	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in the antiparallel orientation of E1.
24	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in the antiparallel orientation of E1.
25	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in the antiparallel orientation of E1.
26	71	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in the antiparallel orientation of E1.
27	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 9) inserted in E1.
28	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 11) inserted in E1.
29	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$ , the vector contains the cis-acting packaging sequence of the wild type

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		adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 13) inserted in E1.
30	74	The claim is directed to an adenoviral vector that is at least partially deleted of $\Delta E1$ and $\Delta E3$ , the vector contains the cis-acting packaging sequence of the wild type adenovirus genome, and a gene which encodes an HIV Nef protein (SEQ ID NO: 15) inserted in E1.
31	76-80	The claims are directed to a method of making and harvesting of a recombinant adenoviral particle that contains a gene encoding an HIV Nef protein.
32	81, 84, 85	The claims are directed to a method of generating a cellular mediated immune response to HIV Nef with the recombinant adenoviral particle.
33	82, 83	The claims are directed to a method of generating a cellular mediated immune response to HIV Nef with the recombinant adenoviral particle <u>in addition to</u> administering a DNA plasmid vaccine.
34	86a	The claim is drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from three individual vectors.
35	86b, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from one individual vectors.
36	86c, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>nef-pol</i> fusion and one expressing <i>gag</i> .
37	86d, 87, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>gag-pol</i> fusion and one expressing <i>nef</i> .
38	86e, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from two individual vectors, one expressing <i>nef-gag</i> fusion and one expressing <i>pol</i> .
39	86f, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> , <i>pol</i> and <i>nef</i> are expressed from a single vectors as a fusion protein.
40	86g, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed from two individual vectors.
41	86h, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed individually from one vector.
42	86i, 88	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed from two individual vectors.
43	86j, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed from individually from one vector.
44	86k, 88	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed individually from one vector.
45	86l, 88, 89	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed individually from one vector.
46	86m, 88	The claims are drawn to a multivalent vaccine wherein <i>gag</i> and <i>pol</i> are expressed as a fusion protein from one vector.
47	86n, 88	The claims are drawn to a multivalent vaccine wherein <i>pol</i> and <i>nef</i> are expressed as a fusion protein from one vector.
48	86o, 88	The claims are drawn to a multivalent vaccine wherein <i>nef</i> and <i>gag</i> are expressed as a fusion protein from one vector.

The inventions listed as Groups 1-48 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups 1-33 appears to be a recombinant adenoviral vector wherein the adenoviral vector is at least partially deleted in E1 but the vector may contain more deletions, the vector contains wild type sequences including packaging signals and a gene encoding a heterologous HIV protein or fragments thereof. Erd et al. (WO 96/39178) disclose a recombinant adenoviral vector that is deleted in E1 and partially deleted in E3, the remainder of the adenoviral vector contains wild type sequences. The vector additionally contains an insertion of a heterologous protein which includes HIV proteins (see abstract and claims 1 and 5). Therefore, the technical feature linking the inventions of groups 1-45 does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of the following groups 1-3, 7-15, 19-30 and 34-48 is considered to be the combination of sequences that is disclosed in each group, see individual claim groupings above for the different sequences. The DNA disclosed in each group is made up of a different sequence having a different structure and different function.

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(72) Inventors; and

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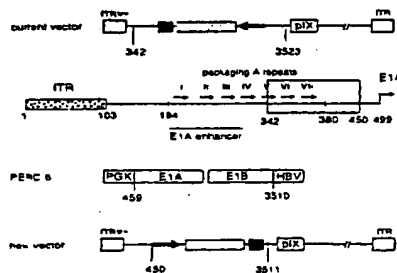
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(54) Title: ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING CODON OPTIMIZED HIV1-GAG, POL, NEF AND MODIFICATIONS



Modifications made to the current adenovector backbone in the generation of the new vector.

(57) Abstract: First generation adenoviral vectors and associated recombinant adenovirus-based HIV vaccines which show enhanced stability and growth properties and greater cellular-mediated immunity are described within this specification. These adenoviral vectors are utilized to generate and produce through cell culture various adenoviral-based HIV-1 vaccines which contain HIV-1 gag, HIV-1 pol and/or HIV-1 nef polynucleotide pharmaceutical products, and biologically relevant modifications thereof. These adenovirus vaccines, when directly introduced into living vertebrate tissue, preferably a mammalian host such as a human or a non-human mammal of commercial or domestic veterinary importance, express the HIV-1 Gag, Pol and/or Nef protein or biologically modification thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding HIV-1 Gag, encoding codon optimized HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease, reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The adenoviral vaccines of the present invention, when administered alone or in a combined modality regime, will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

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## TITLE OF THE INVENTION

ENHANCED FIRST GENERATION ADENOVIRUS VACCINES EXPRESSING  
CODON OPTIMIZED HIV1-GAG, POL, NEF AND MODIFICATIONS

## 5 CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit, under 35 U.S.C. §119(e), of U.S.  
provisional applications 60/233,180, 60/279,056, and Attorney Docket 20867PV2  
(serial number unassigned), filed September 15, 2000, March 27, 2001, and  
September 7, 2001, respectively.

10

## STATEMENT REGARDING FEDERALLY-SPONSORED R&amp;D

Not Applicable

## REFERENCE TO MICROFICHE APPENDIX

15

Not Applicable

## FIELD OF THE INVENTION

The present invention relates to recombinant, replication-deficient first  
generation adenovirus vaccines found to exhibit enhanced growth properties and  
20 greater cellular-mediated immunity as compared to other replication-deficient vectors.  
The invention also relates to the associated first generation adenoviral vectors  
described herein, which, through the incorporation of additional 5' adenovirus  
sequence, enhance large scale production efficiency of the recombinant, replication-  
defective adenovirus described herein. Another aspect of the instant invention is the  
25 surprising discovery that the intron A portion of the human cytomegalovirus (hCMV)  
promoter constitutes a region of instability in adenoviral vector constructs. Removal  
of this region from adenoviral expression constructs results in greatly improved vector  
stability. Therefore, improved vectors expressing a transgene under the control of an  
intron A-deleted CMV promoter constitute a further aspect of this invention. These  
30 adenoviral vectors are useful for generating recombinant adenovirus vaccines against  
human immunodeficiency virus (HIV). In particular, the first generation adenovirus  
vectors disclosed herein are utilized to construct and generate adenovirus-based HIV-  
1 vaccines which contain HIV-1 Gag, HIV-1 Pol and/or HIV-1 Nef polynucleotide  
pharmaceutical products, and biologically active modifications thereof. Host  
35 administration of the recombinant, replication-deficient adenovirus vaccines described  
herein results in expression of HIV-1 Gag, HIV-1- Pol and/or Nef protein or

immunologically relevant modifications thereof, inducing a cellular immune response which specifically recognizes HIV-1. The exemplified polynucleotides of the present invention are synthetic DNA molecules encoding codon optimized HIV-1 Gag, HIV-1 Pol, derivatives of optimized HIV-1 Pol (including constructs wherein protease, reverse transcriptase, RNase H and integrase activity of HIV-1 Pol is inactivated), HIV-1 Nef, and derivatives of optimized HIV-1 Nef, including nef mutants which effect wild type characteristics of Nef, such as myristylation and down regulation of host CD4. The HIV adenovirus vaccines of the present invention, when administered alone or in a combined modality and/or prime/boost regimen, will offer a prophylactic advantage to previously uninfected individuals and/or provide a therapeutic effect by reducing viral load levels within an infected individual, thus prolonging the asymptomatic phase of HIV-1 infection.

#### BACKGROUND OF THE INVENTION

Human Immunodeficiency Virus-1 (HIV-1) is the etiological agent of acquired human immune deficiency syndrome (AIDS) and related disorders. HIV-1 is an RNA virus of the Retroviridae family and exhibits the 5' LTR-*gag-pol-env*-LTR 3' organization of all retroviruses. The integrated form of HIV-1, known as the provirus, is approximately 9.8 Kb in length. Each end of the viral genome contains flanking sequences known as long terminal repeats (LTRs). The HIV genes encode at least nine proteins and are divided into three classes; the major structural proteins (Gag, Pol, and Env), the regulatory proteins (Tat and Rev); and the accessory proteins (Vpu, Vpr, Vif and Nef).

The *gag* gene encodes a 55-kilodalton (kDa) precursor protein (p55) which is expressed from the unspliced viral mRNA and is proteolytically processed by the HIV protease, a product of the *pol* gene. The mature p55 protein products are p17 (matrix), p24 (capsid), p9 (nucleocapsid) and p6.

The *pol* gene encodes proteins necessary for virus replication; a reverse transcriptase, a protease, integrase and RNase H. These viral proteins are expressed as a Gag-Pol fusion protein, a 160 kDa precursor protein which is generated via a ribosomal frame shifting. The viral encoded protease proteolytically cleaves the Pol polypeptide away from the Gag-Pol fusion and further cleaves the Pol polypeptide to the mature proteins which provide protease (Pro, P10), reverse transcriptase (RT, P50), integrase (IN, p31) and RNase H (RNase, p15) activities.

The *nef* gene encodes an early accessory HIV protein (Nef) which has been shown to possess several activities such as down regulating CD4 expression, disturbing T-cell activation and stimulating HIV infectivity.

The *env* gene encodes the viral envelope glycoprotein that is translated as a  
5 160-kilodalton (kDa) precursor (gp160) and then cleaved by a cellular protease to yield the external 120-kDa envelope glycoprotein (gp120) and the transmembrane 41-kDa envelope glycoprotein (gp41). Gp120 and gp41 remain associated and are displayed on the viral particles and the surface of HIV-infected cells.

The *tat* gene encodes a long form and a short form of the Tat protein, a RNA  
10 binding protein which is a transcriptional transactivator essential for HIV-1 replication.

The *rev* gene encodes the 13 kDa Rev protein, a RNA binding protein. The Rev protein binds to a region of the viral RNA termed the Rev response element (RRE). The Rev protein promotes transfer of unspliced viral RNA from the nucleus  
15 to the cytoplasm. The Rev protein is required for HIV late gene expression and in turn, HIV replication.

Gp120 binds to the CD4/chemokine receptor present on the surface of helper T-lymphocytes, macrophages and other target cells in addition to other co-receptor molecules. X4 (macrophage tropic) virus show tropism for CD4/CXCR4 complexes  
20 while a R5 (T-cell line tropic) virus interacts with a CD4/CCR5 receptor complex. After gp120 binds to CD4, gp41 mediates the fusion event responsible for virus entry. The virus fuses with and enters the target cell, followed by reverse transcription of its single stranded RNA genome into the double-stranded DNA via a RNA dependent DNA polymerase. The viral DNA, known as provirus, enters the cell nucleus, where  
25 the viral DNA directs the production of new viral RNA within the nucleus, expression of early and late HIV viral proteins, and subsequently the production and cellular release of new virus particles. Recent advances in the ability to detect viral load within the host shows that the primary infection results in an extremely high generation and tissue distribution of the virus, followed by a steady state level of virus  
30 (albeit through a continual viral production and turnover during this phase), leading ultimately to another burst of virus load which leads to the onset of clinical AIDS. Productively infected cells have a half life of several days, whereas chronically or latently infected cells have a 3-week half life, followed by non-productively infected cells which have a long half life (over 100 days) but do not significantly contribute to  
35 day to day viral loads seen throughout the course of disease.

Destruction of CD4 helper T lymphocytes, which are critical to immune defense, is a major cause of the progressive immune dysfunction that is the hallmark of HIV infection. The loss of CD4 T-cells seriously impairs the body's ability to fight most invaders, but it has a particularly severe impact on the defenses against viruses, fungi, parasites and certain bacteria, including mycobacteria.

Effective treatment regimens for HIV-1 infected individuals have become available recently. However, these drugs will not have a significant impact on the disease in many parts of the world and they will have a minimal impact in halting the spread of infection within the human population. As is true of many other infectious diseases, a significant epidemiologic impact on the spread of HIV-1 infection will only occur subsequent to the development and introduction of an effective vaccine. There are a number of factors that have contributed to the lack of successful vaccine development to date. As noted above, it is now apparent that in a chronically infected person there exists constant virus production in spite of the presence of anti-HIV-1 humoral and cellular immune responses and destruction of virally infected cells. As in the case of other infectious diseases, the outcome of disease is the result of a balance between the kinetics and the magnitude of the immune response and the pathogen replicative rate and accessibility to the immune response. Pre-existing immunity may be more successful with an acute infection than an evolving immune response can be with an established infection. A second factor is the considerable genetic variability of the virus. Although anti-HIV-1 antibodies exist that can neutralize HIV-1 infectivity in cell culture, these antibodies are generally virus isolate-specific in their activity. It has proven impossible to define serological groupings of HIV-1 using traditional methods. Rather, the virus seems to define a serological "continuum" so that individual neutralizing antibody responses, at best, are effective against only a handful of viral variants. Given this latter observation, it would be useful to identify immunogens and related delivery technologies that are likely to elicit anti-HIV-1 cellular immune responses. It is known that in order to generate CTL responses antigen must be synthesized within or introduced into cells, subsequently processed into small peptides by the proteasome complex, and translocated into the endoplasmic reticulum/Golgi complex secretory pathway for eventual association with major histocompatibility complex (MHC) class I proteins. CD8<sup>+</sup> T lymphocytes recognize antigen in association with class I MHC via the T cell receptor (TCR) and the CD8 cell surface protein. Activation of naive CD8<sup>+</sup> T cells into activated effector or memory cells generally requires both TCR engagement of antigen as described above as well as engagement of costimulatory proteins. Optimal

induction of CTL responses usually requires "help" in the form of cytokines from CD4<sup>+</sup> T lymphocytes which recognize antigen associated with MHC class II molecules via TCR and CD4 engagement.

European Patent Applications 0 638 316 (Published February 15, 1995) and 0  
5 586 076 (Published March 9, 1994), (both assigned to American Home Products Corporation) describe replicating adenovirus vectors carrying an HIV gene, including *env* or *gag*. Various treatment regimens were used with chimpanzees and dogs, some of which included booster adenovirus or protein plus alum treatments.

Replication-defective adenoviral vectors harboring deletions in the E1 region  
10 are known, and recent adenoviral vectors have incorporated the known packaging repeats into these vectors; e.g., see EP 0 707 071, disclosing, *inter alia*, an adenoviral vector deleted of E1 sequences from base pairs 459 to 3328; and U.S. Patent No. 6,033,908, disclosing, *inter alia*, an adenoviral vector deleted of base pairs 459-3510. The packaging efficiency of adenovirus has been taught to depend on the number of  
15 incorporated individual A (packaging) repeats; see, e.g., Gräble and Hearing, 1990 *J. Virol.* 64(5):2047-2056; Gräble and Hearing, 1992 *J. Virol.* 66(2):723-731.

Larder, et al., (1987, *Nature* 327: 716-717) and Larder, et al., (1989, *Proc. Natl. Acad. Sci.* 86: 4803-4807) disclose site specific mutagenesis of HIV-1 RT and the effect such changes have on *in vitro* activity and infectivity related to interaction  
20 with known inhibitors of RT.

Davies, et al. (1991, *Science* 252:, 88-95) disclose the crystal structure of the RNase H domain of HIV-1 Pol.

Schatz, et al. (1989, *FEBS Lett.* 257: 311-314) disclose that mutations Glu478Gln and His539Phe in a complete HIV-1 RT/RNase H DNA fragment results  
25 in defective RNase activity without effecting RT activity.

Mizrahi, et al. (1990, *Nucl. Acids. Res.* 18: pp. 5359-5353) disclose additional mutations Asp443Asn and Asp498Asn in the RNase region of the *pol* gene which also results in defective RNase activity. The authors note that the Asp498Asn mutant was difficult to characterize due to instability of this mutant protein.

Leavitt, et al. (1993, *J. Biol. Chem.* 268: 2113-2119) disclose several  
30 mutations, including a Asp64Val mutation, which show differing effect on HIV-1 integrase (IN) activity.

Wiskerchen, et al. (1995, *J. Virol.* 69: 376-386) disclose single and double mutants, including mutation of aspartic acid residues which effect HIV-1 IN and viral  
35 replication functions.

It would be of great import in the battle against AIDS to produce a prophylactic- and/or therapeutic-based HIV vaccine which generates a strong cellular immune response against an HIV infection. The present invention addresses and meets these needs by disclosing a class of adenovirus vaccines which, upon host administration, express codon optimized and modified versions of the HIV-1 genes, *gag*, *pol* and *nef*. These recombinant, replication-defective adenovirus vaccines may be administered to a host, such as a human, alone or as part of a combined modality regimen and/or prime-boost vaccination regimen with components of the present invention and/or a distinct viral HIV DNA vaccine, non-viral HIV DNA vaccine, HIV subunit vaccine, an HIV whole killed vaccine and/or a live attenuated HIV vaccine.

#### SUMMARY OF THE INVENTION

The present invention relates to enhanced replication-defective recombinant adenovirus vaccine vectors and associated recombinant, replication-deficient adenovirus vaccines which encode various forms of HIV-1 Gag, HIV-1 Pol, and/or HIV-1 Nef, including immunologically relevant modifications of HIV-1 Gag, HIV-1 Pol and HIV-1 Nef. The adenovirus vaccines of the present invention express HIV antigens and provide for improved cellular-mediated immune responses upon host administration. Potential vaccinees include but are not limited to primates and especially humans and non-human primates, and also include any non-human mammal of commercial or domestic veterinary importance. An effect of the improved recombinant adenovirus-based vaccines of the present invention should be a lower transmission rate to previously uninfected individuals (i.e., prophylactic applications) and/or reduction in the levels of the viral loads within an infected individual (i.e., therapeutic applications), so as to prolong the asymptomatic phase of HIV-1 infection. In particular, the present invention relates to adenoviral-based vaccines which encode various forms of codon optimized HIV-1 Gag (including but in no way limited to p55 versions of codon optimized full length (FL) Gag and tPA-Gag fusion proteins), HIV-1 Pol, HIV-1 Nef, and selected modifications of immunological relevance. The administration, intracellular delivery and expression of these adenovirus vaccines elicit a host CTL and Th response. The preferred replication-defective recombinant adenoviral vaccine vectors include but are not limited to synthetic DNA molecules which (1) encode codon optimized versions of wild type HIV-1 Gag; (2) encode codon optimized versions of HIV-1 Pol; (3) encode codon optimized versions of HIV-1 Pol fusion proteins; (4) encode codon optimized versions of modified HIV-1 Pol proteins and fusion proteins, including but not limited

to *pol* modifications involving residues within the catalytic regions responsible for RT, RNase and IN activity within the host cell; (5) encode codon optimized versions of wild type HIV-1 Nef; (6) codon optimized versions of HIV-1 Nef fusion proteins; and/or (7) codon optimized versions of HIV-1 Nef derivatives, including but not limited to *nef* modifications involving introduction of an amino-terminal leader sequence, removal of an amino-terminal myristylation site and/or introduction of dileucine motif mutations. The Nef-based fusion and modified proteins, disclosed within this specification and expressed from an adenoviral-based vector vaccine this specification, may possess altered trafficking and/or host cell function while retaining the ability to be properly presented to the host MHC I complex and in turn elicit a host CTL and Th response. Examples of HIV-1 Gag, Pol and/or Nef fusion proteins include but are not limited to fusion of a leader or signal peptide at the NH<sub>2</sub>-terminal portion of the viral antigen coding region. Such a leader peptide includes but is not limited to a tPA leader peptide.

The adenoviral vector utilized in construction of the HIV-1 Gag-, HIV-1 Pol- and/or HIV-1 Nef- based vaccines of the present invention may comprise any replication-defective adenoviral vector which provides for enhanced genetic stability of the recombinant adenoviral genome through large scale production and purification of the recombinant virus. In other words, an HIV-1 Gag-, Pol- or Nef-based adenovirus vaccine of the present invention is a purified recombinant, replication-defective adenovirus which is shown to be genetically stable through multiple passages in cell culture and remains so during large scale production and purification procedures. Such a recombinant adenovirus vector and harvested adenovirus vaccine lends itself to large scale dose filling and subsequent worldwide distribution procedures which will be demanded of an efficacious monovalent or multivalent HIV vaccine. The present invention meets this basic requirement with description of a replication-defective adenoviral vector and vectors derived therefrom, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 of the wildtype adenovirus genome. A preferred embodiment of the instant invention comprises base pairs 1-450 of a wildtype adenovirus. In other preferred embodiments, the replication -defective adenoviral vector has, in addition thereto, a region 3' to the E1-deleted region comprising base pairs 3511-3523. Basepairs 342-450 (more particularly, 400-450) constitute an extension of the 5'-region of previously disclosed vectors carrying viral antigens, particularly HIV antigens (see, e.g., PCT International Application PCT/US00/18332, published

January 11, 2001 (WO 01/02067), which claims priority to U.S. Provisional Application Serial Nos. 60/142,631 and 60/148,981, filed 7/6/1999 and 8/13/1999, respectively; these documents herein incorporated by reference. Applicants have found that extending the 5' region further into the E1 gene into the disclosed vaccine  
5 vectors incorporated elements found to be important in optimizing the packaging of the virus.

As compared to previous vectors not comprising basepairs from about 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 of the wildtype adenovirus genome, vectors comprising the above region exhibited enhanced  
10 growth characteristics, with approximately 5-10 fold greater amplification rates, a more potent virus effect, allowing lower doses of virus to be used to generate equivalent immunity; and a greater cellular-mediated immune response than replication-deficient vectors not comprising this region (basepairs 1-450). Even more  
15 large-scale production, particularly those comprising an expression cassette under the control of a hCMV promoter devoid of intron A. This is because Applicants have surprisingly found that the intron A portion of the hCMV promoter constituted a region of instability when employed in adenoviral vectors. Applicants have, therefore, identified an enhanced adenoviral vector which is particularly suited for use  
20 in gene therapy and nucleotide-based vaccine vectors which, favorably, lends itself to large scale propagation.

A preferred embodiment of this invention is a replication-defective adenoviral vector in accordance with the above description wherein the gene is inserted in the form of a gene expression cassette comprising (a) a nucleic acid encoding a protein or  
25 biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and, (c) a transcription terminator.

In preferred embodiments, the E1 gene, other than that contained within basepairs 1-450 or, alternatively, that contained within base pairs 1-450 and 3511-  
30 3523 has been deleted from the adenoviral vector, and the gene expression cassette has replaced the deleted E1 gene. In other preferred embodiments, the replication defective adenovirus genome does not have a functional E3 gene, or the E3 gene has been deleted. Most preferably, the E3 region is present within the adenoviral genome. Further preferred embodiments are wherein the gene expression cassette is in an E1  
35 anti-parallel (transcribed in a 3' to 5' direction relative to the vector backbone)

orientation or, more preferably, an E1 parallel (transcribed in a 5' to 3' direction relative to the vector backbone) orientation.

Further embodiments relate to a shuttle plasmid vector comprising: an adenoviral portion and a plasmid portion, wherein said adenovirus portion comprises:

- 5 a) a replication defective adenovirus genome, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 (preferably, 1-450) of the wildtype adenovirus genome and, preferably, in addition thereto, basepairs 3511-3523 of a wildtype adenovirus sequence; and b) a gene  
10 expression cassette comprising: (a) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and (c) a transcription terminator and/or a polyadenylation site.

- Other aspects of this invention include a host cell comprising said adenoviral  
15 vectors and/or said shuttle plasmid vectors; vaccine compositions comprising said vectors; and methods of producing the vectors comprising (a) introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and (b) harvesting the resultant adenoviral vectors.

- To this end, the present invention particularly relates to harvested  
20 recombinant, replication defective virus derived from a host cell, such as but not limited to 293 cells or PER.C6<sup>®</sup> cells, including but not limited to harvested virus related to any of the MRKAd5 vector backbones, with or without an accompanying transgene, including but not limited to the HIV-1 antigens described herein. An HIV-1 vaccine is represented by any harvested, recombinant adenovirus material  
25 which expresses any one or more of the HIV-1 antigens disclosed herein. This harvested material may then be purified, formulated and stored prior to host administration.

- Another aspect of this invention is a method of generating a cellular immune response against a protein in an individual comprising administering to the individual  
30 an adenovirus vaccine vector comprising:

- a) a recombinant, replication defective adenoviral vector, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting adenovirus packaging region from about base pair 1 to between from about base pair 342 (more preferably, 400) to about base pair 458 (preferably, 1-450) and, preferably in addition thereto,  
35 base pairs 3511-3523 of a wildtype adenovirus sequence, and,

b) a gene expression cassette comprising: (i) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (ii) a heterologous promoter operatively linked to the nucleic acid of part a); and (iii) a transcription terminator and/or a polyadenylation site.

5 In view of the efficacious nature of the adenoviral and/or DNA plasmid vaccines described herein, the present invention relates to all methodology regarding administration of one or more of these adenoviral and/or DNA plasmid vaccines to provide effective immunoprophylaxis, to prevent establishment of an HIV-1 infection following exposure to this virus, or as a post-HIV infection therapeutic vaccine to  
10 mitigate the acute HIV-1 infection so as to result in the establishment of a lower virus load with beneficial long term consequences. As discussed herein, such a treatment regimen may include a monovalent or multivalent composition, various combined modality applications, and/or a prime/boost regimen to as to optimize antigen expression and a concomitant cellular-mediated and/or humoral immune response  
15 upon inoculation into a living vertebrate tissue. Therefore, the present invention provides for methods of using the adenoviral and/or DNA plasmid vaccines disclosed herein within the various parameters disclosed herein as well as any additional parameters known in the art, which, upon introduction into mammalian tissue induces intracellular expression of the gag, pol and/or nef-based vaccines.

20 To this end, the present invention relates in part to methods of generating a cellular immune response in a vaccinee, preferably a human vaccinee, wherein the individual is given more than one administration of adenovirus vaccine vector, and it may be given in a regimen accompanied by the administration of a plasmid vaccine. The plasmid vaccine (also referred to herein as a "DNA plasmid vaccine" or "vaccine plasmid" comprises a nucleic acid encoding a protein or an immunologically relevant  
25 portion thereof, a heterologous promoter operably linked to the nucleic acid sequence, and a transcription terminator or a polyadenylation signal (such as bGH or SPA, respectively). There may be a predetermined minimum amount of time separating the administrations. The individual can be given a first dose of plasmid vaccine, and then  
30 a second dose of plasmid vaccine. Alternatively, the individual may be given a first dose of adenovirus vaccine, and then a second dose of adenovirus vaccine. In other embodiments, the plasmid vaccine is administered first, followed after a time by administration of the adenovirus vaccine. Conversely, the adenovirus vaccine may be administered first, followed by administration of plasmid vaccine after a time. In  
35 these embodiments, an individual may be given multiple doses of the same adenovirus serotype in either viral vector or plasmid form, or the virus may be of

differing serotypes. In the alternative, a viral antigen of interest can be first delivered via a viral vaccine other than an adenovirus-based vaccine, and then followed with the adenoviral vaccine disclosed. Alternative viral vaccines include but are not limited to pox virus and venezuelan equine encephalitis virus.

5           The present invention also relates to multivalent adenovirus vaccine compositions which comprise Gag, Pol and Nef components described herein; see, e.g., Example 29 and Table 25. Such compositions will provide for an enhanced cellular immune response subsequent to host administration, particularly given the genetic diversity of human MHCs and of circulating virus. Examples, but not  
10 limitations, include MRKAd5-vector based multivalent vaccine compositions which provide for a divalent (i.e., gag and nef, gag and pol, or pol and nef components) or a trivalent vaccine (i.e., gag, pol and nef components) composition. Such a multivalent vaccine may be filled for a single dose or may consist of multiple inoculations of each individually filled component; and may in addition be part of a prime/boost regimen  
15 with viral or non-viral vector vaccines as introduced in the previous paragraph. To this end, preferred compositions are MRKAd5 adenovirus used in combination with multiple, distinct HIV antigen classes. Each HIV antigen class is subject to sequence manipulation, thus providing for a multitude of potential vaccine combinations; and such combinations are within the scope of the present invention. The utilization of  
20 such combined modalities vaccine formulation and administration increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a single modality regimen.

          The concept of a "combined modality" as disclosed herein also covers the alternative mode of administration whereby multiple HIV-1 viral antigens may be  
25 ligated into a proper shuttle plasmid for generation of a pre-adenoviral plasmid comprising multiple open reading frames. For example, a trivalent vector may comprise a gag-pol-nef fusion, in either a E3(-) or E3(+) background, preferably a E3 deleted backbone, or possibly a "2+1" divalent vaccine, such as a gag-pol fusion (i.e., codon optimized p55 gag and inactivated optimized pol; Example 29 and Table 25)  
30 within the same MRKAd5 backbone, with each open reading frame being operatively linked to a distinct promoter and transcription termination sequence. Alternatively, the two open reading frames may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES). Therefore, a multivalent vaccine delivered as a single, or possibly a second  
35 harvested recombinant, replication-deficient adenovirus is contemplated as part of the present invention.

Therefore, the adenoviral vaccines and plasmid DNA vaccines of this invention may be administered alone, or may be part of a prime and boost administration regimen. A mixed modality priming and booster inoculation scheme will result in an enhanced immune response, particularly if pre-existing anti-vector immune responses are present. This one aspect of this invention is a method of priming a subject with the plasmid vaccine by administering the plasmid vaccine at least one time, allowing a predetermined length of time to pass, and then boosting by administering the adenoviral vaccine. Multiple primings typically, 1-4, are usually employed, although more may be used. The length of time between priming and boost may typically vary from about four months to a year, but other time frames may be used. In experiments with rhesus monkeys, the animals were primed four times with plasmid vaccines, then were boosted 4 months later with the adenoviral vaccine. Their cellular immune response was notably higher than that of animals which had only received adenoviral vaccine. The use of a priming regimen may be particularly preferred in situations where a person has a pre-existing anti-adenovirus immune response.

It is an object of the present invention to provide for enhanced replication-defective recombinant adenoviral vaccine vector backbones. These recombinant adenoviral backbones may accept one or more transgenes, which may be passaged through cell culture for growth, amplification and harvest.

It is a further object to provide for enhanced replication-defective recombinant adenoviral vaccine vectors which encode various transgenes.

It is also an object of the present invention to provide for a harvested recombinant, replication-deficient adenovirus which shows enhanced growth and amplification rates while in combination with increased virus stability after continuous passage in cell culture. Such a recombinant adenovirus is particularly suited for use in gene therapy and nucleotide-based vaccine vectors which, favorably, lends itself to large scale propagation.

To this end, it is an object of the present invention to provide for (1) enhanced replication-defective recombinant adenoviral vaccine vectors as described herein which encode various forms of HIV-1 Gag, HIV-1 Pol, and/or HIV-1 Nef, including immunologically relevant modifications of HIV-1 Gag, HIV-1 Pol and HIV-1 Nef, and (2) harvested, purified recombinant replication-deficient adenovirus generated by passage of the adenoviral vectors of (1) through one or multiple passages through cell culture, including but not limited to passage through 293 cells or PER.C6® cells.

It is also an object of the present invention to provide for recombinant adenovirus harvested by one or multiple passages through cell culture. As relating to recombinant adenoviral vaccine vector, this recombinant virus is harvested and formulated for subsequent host administration.

5 It is also an object of the present invention to provide for replication-defective adenoviral vectors wherein at least one gene is inserted in the form of a gene expression cassette comprising (a) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (b) a heterologous promoter operatively linked to the nucleic acid of part a); and, (c) a transcription terminator.

10 It is also an object of the present invention to provide for a host cell comprising said adenoviral vectors and/or said shuttle plasmid vectors; vaccine compositions comprising said vectors; and methods of producing the vectors comprising (a) introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and (b) harvesting the resultant adenoviral vectors.

15 It is a further object of the present invention to provide for methods of generating a cellular immune response against a protein in an individual comprising administering to the individual an adenovirus vaccine vector comprising a) a replication defective adenoviral vector, at least partially deleted in E1, comprising a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between from about base pair  
20 342 (more preferably, 400) to about 450 (preferably, 1-450) and, preferably, 3511-3523 of a wildtype adenovirus sequence, and, b) a gene expression cassette comprising: (i) a nucleic acid encoding a protein or biologically active and/or immunologically relevant portion thereof; (ii) a heterologous promoter operatively linked to the nucleic acid of part a); and (iii) a transcription terminator and/or a  
25 polyadenylation site.

It is also an object of the present invention to provide various alternatives for vaccine administration regimes, namely administration of one or more adenoviral and/or DNA plasmid vaccines described herein to provide effective immunoprophylaxis for uninfected individuals or a therapeutic treatment for HIV  
30 infected patients. Such processes include but are not limited to multivalent HIV-1 vaccine compositions, various combined modality regimes as well as various prime/boost alternatives. These methods of administration, relating to vaccine composition and/or scheduled administration, will increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a  
35 single modality regimen.

As used throughout the specification and claims, the following definitions and abbreviations are used:

"HAART" refers to -- highly active antiretroviral therapy --.

"first generation" vectors are characterized as being replication-defective.

- 5 They typically have a deleted or inactivated E1 gene region, and preferably have a deleted or inactivated E3 gene region as well.

"AEX" refers to Anion Exchange chromatography.

"QPA" refers to Quick PCR-based Potency Assay.

"bps" refers to basepairs.

- 10 "s" or "str" denotes that the transgene is in the E1 parallel or "straight" orientation.

"PBMCs" refers to peripheral blood monocyte cells.

"FL" refers to full length.

"FLgag" refers to a full-length optimized gag gene, as shown in Figure 2.

- 15 "Ad5-Flgag" refers to an adenovirus serotype 5 replication deficient virus which carries an expression cassette which comprises a full length optimized gag gene under the control of a CMV promoter.

- "Promoter" means a recognition site on a DNA strand to which an RNA polymerase binds. The promoter forms an initiation complex with RNA polymerase to initiate and drive transcriptional activity. The complex can be modified by activating sequences such as enhancers or inhibiting sequences such as silencers.
- 20

"Leader" means a DNA sequence at the 5' end of a structural gene which is transcribed along with the gene. This usually results a protein having an N-terminal peptide extension, often referred to as a pro-sequences.

- 25 "Intron" means a section of DNA occurring in the middle of a gene which does not code for an amino acid in the gene product. The precursor RNA of the intron is excised and is therefore not transcribed into mRNA not translated into protein.

- "Immunologically relevant" or "biologically active" means (1) with regards to a viral protein, that the protein is capable, upon administration, of eliciting a measurable immune response within an individual sufficient to retard the propagation and/or spread of the virus and/or to reduce the viral load present within the individual; or (2) with regards to a nucleotide sequence, that the sequence is capable of encoding for a protein capable of the above.
- 30

- "Cassette" refers to a nucleic acid sequence which is to be expressed, along with its transcription and translational control sequences. By changing the cassette, a vector can express a different sequence.
- 35

"bGHpA" refers to the bovine growth hormone transcription terminator/polyadenylation sequence.

"tPAgag" refers to a fusion between the leader sequence of the tissue plasminogen activator leader sequence and an optimized HIV gag gene, as exemplified in Figure 30A-B, whether in a DNA or adenovirus-based vaccine vector.

Where utilized, "IA" or "inact" refers to an inactivated version of a gene (e.g. IApol).

"MCS" is "multiple cloning site".

In general, adenoviral constructs, gene constructs are named by reference to the genes contained therein. For example:

"Ad5 HIV-1 gag", also referred to as the original HIV-1 gag adenoviral vector, is a vector containing a transgene cassette composed of a hCMV intron A promoter, the full length version of the human codon-optimized HIV-1 gag gene, and the bovine growth hormone polyadenylation signal. The transgene was inserted in the E1 antiparallel orientation in an E1 and E3 deleted adenovector.

"MRK Ad5 HIV-1 gag" also referred to as "MRKAd5gag" or "Ad5gag2" is an adenoviral vector taught herein which is deleted of E1, comprises basepairs 1-450 and 3511-3523, and has a human codon-optimized HIV-1 gene in an E1 parallel orientation under the control of a CMV promoter without intron A. The construct also comprises a bovine growth hormone polyadenylation signal.

"pV1JnsHIVgag", also referred to as "HIVFLgagPR9901", is a plasmid comprising the CMV immediate-early (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone.

"pV1JnsCMV(no intron)-FLgag-bGHpA" is a plasmid derived from pV1JnsHIVgag which is deleted of the intron A portion of CMV and which comprises the full length HIV gag gene. This plasmid is also referred to as "pV1JnsHIVgag-bGHpA", pV1Jns-hCMV-FL-gag-bGHpA" and "pV1JnsCMV(no intron) + FLgag + bGHpA".

"pV1JnsCMV(no intron)-FLgag-SPA" is a plasmid of the same composition as pV1JnsCMV(no intron)-FLgag-bGHpA except that the SPA termination sequence replaces that of bGHpA. This plasmid is also referred to as "pV1Jns-HIVgag-SPA" and pV1Jns-hCMV-FLgag-SPA".

"pdelE1sp1A" is a universal shuttle vector with no expression cassette (i.e., no promoter or polyA). The vector comprises wildtype adenovirus serotype 5 (Ad5) sequences from bp 1 to bp 341 and bp 3524 to bp 5798, and has a multiple cloning

site between the Ad5 sequences ending 341 bp and beginning 3524 bp. This plasmid is also referred to as the original Ad 5 shuttle vector.

"MRKpdeIE1sp1A" or "MRKpdeIE1(Pac/pIX/pack450)" or

5 "MRKpdeIE1(Pac/pIX/pack450)Cla1" is a universal shuttle vector with no expression cassette (i.e. no promoter or polyA) comprising wildtype adenovirus serotype 5 (Ad5) sequences from bp1 to bp450 and bp 3511 to bp 5798. The vector has a multiple cloning site between the Ad5 sequence ending 450 bp and beginning 3511 bp. This shuttle vector may be used to insert the CMV promoter and the bGHpA fragments in both the straight ("str". or E1 parallel) orientation or in the opposite (opp. or E1  
10 antiparallel) orientation)

"MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.)" is still another shuttle vector which is the modified vector that contains the CMV promoter (no intronA) and the bGHpA fragments. The expression unit containing the hCMV promoter (no intron A) and the bovine growth hormone polyadenylation signal has  
15 been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*II site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1/E3+)Cla1 pre-plasmid. This shuttle vector, as shown in Figures 22 and 23, was used to insert the respective LAPol and G2A,LLAA nef genes directly into.

20 "MRKpdeIE1-CMV(no intron)-FLgag-bGHpA" is a shuttle comprising Ad5 sequences from basepairs 1-450 and 3511-5798, with an expression cassette containing human CMV without intron A, the full-length human codon-optimized HIV gag gene and bovine growth hormone polyadenylation signal. This plasmid is also referred to as "MRKpdeIE1 shuttle +hCMV-FL-gag-BGHpA"

25 "MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA" is an adenoviral vector comprising all Ad5 sequences except those nucleotides encompassing the E1 region (from 451-3510), a human CMV promoter without intron A, a full-length human codon-optimized HIV gag gene, and a bovine growth hormone polyadenylation signal. This vector is also referred to as "MRKpAdHVE3 + hCMV-FL-gag-  
30 BGHpA", "MRKpAd5HIV-1gag", "MRKpAd5gag", "pMRKAd5gag" or "pAd5gag2".

"pV1Jns-HIV-pol inact(opt)" or "pV1Jns-HIV IA pol (opt)" is the inactivated Pol gene (contained within SEQ ID NO:3) cloned into the *Bgl*II site of V1Jns (Figure 17A-C). As noted herein, various derivatives of HIV-1 pol may be cloned into a  
35 plasmid expression vector such as V1Jns or V1Jns-tPA, thus serving directly as DNA vaccine candidates or as a source for subcloning into an appropriate adenoviral vector.

"MRKpdel+hCMVmin+FL-pol+bGHpA(s)" is the "MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHPA(str.)" shuttle mentioned above which contains the IA pol gene is the proper orientation. This shuttle vector is used in a bacterial recombination with MRKpAd(E1-/E3+)ClaI.

5 "MRKpAd+hCMVmin+FL-pol+bGHpA(S)E3+", also referred to herein as "pMRKAd5pol", is the pre-adenovirus plasmid which comprises a CMV-pol inact(opt)-pGHpA construct. The construction of this pre-adenovirus plasmid is shown in Figure 22.

"pV1Jns/nef (G2A,LLAA)" or "V1Jns/opt nef (G2A,LLAA)" comprises  
 10 codon optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175 (SEQ ID NO:13; which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662). This fragment is subcloned into the Bgl II site of V1Jns  
 15 and/or V1Jns-tPA (Figures 16A-B). As noted above for HIV-1 pol, HIV-1 nef constructs may be cloned into a plasmid expression vector such as V1Jns or V1Jns-tPA, thus serving directly as DNA vaccine candidates or as a source for subcloning into an appropriate adenoviral vector.

"MRKpdelE1hCMVminFL-nefBGHPA(s)", also referred to herein as  
 20 "pMRKAd5nef", is the pre-adenovirus plasmid which comprises a CMV-nef (G2A,LLAA) codon optimized sequence. The construction of this pre-adenovirus plasmid is shown in Figure 23.

#### BRIEF DESCRIPTION OF THE FIGURES

25 Figure 1 shows the original HIV-1 gag adenovector (Ad5HIV-1gag). This vector is disclosed in PCT International Application No. PCT/US00/18332 (WO 01/02607) filed July 3, 2000, claiming priority to U.S. Provisional Application Serial No. 60/142,631, filed July 6, 1999 and U.S. Application Serial No. 60/148,981, filed August 13, 1999, all three applications which are hereby incorporated by reference.

30 Figure 2 shows the nucleic acid sequence (SEQ ID NO: 29) of the optimized human HIV-1 gag open reading frame.

Figure 3 shows diagrammatically the new transgene constructs in comparison with the original gag transgene.

35 Figure 4 shows the modifications made to the original adenovector backbone in the generation of the novel vectors of the instant invention.

Figure 5 shows the virus mixing experiments that were carried out to determine the effects of the addition made to the packaging signal region (Expt. #1) and the E3 gene on viral growth (Expt. #2). The bars denote the region of modifications made to the E1 deletion.

Figure 6 shows an autoradiograph of viral DNA analysis following the viral mixing experiments described in Examples 6 and 7.

Figures 7A, 7B and 7C are as follows: Figure 7A shows the hCMV-Flgag-bGHpA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Both E1 parallel and E1 antiparallel transgene orientation are represented. Figure 7B shows the hCMV-Flgag-SPA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Again, both E1 parallel and E1 antiparallel transgene orientation are represented. Figure 7C shows the mCMV-Flgag-bGHpA adenovectors constructed within the MRKpAdHVE3 and MRKpAdHVO adenovector backbones. Once again, both E1 parallel and E1 antiparallel transgene orientation are represented.

Figure 8A shows the experiment designed to test the effect of transgene orientation.

Figure 8B shows the experiments designed to test the effect of polyadenylation signal.

Figure 9 shows viral DNA from the four adenoviral vectors tested (Example 12) at P5, following *Bst*E11 digestion.

Figure 10 shows viral DNA analysis of passages 11 and 12 of MRKpAdHVE3, MRKAd5HIV-1gag, and MRKAd5HIV-1gagE3-.

Figure 11 shows viral DNA analysis (*Hind*III digestion) of passage 6 MRKpAdHVE3 and MRKAd5HIV-1gag used to initiate the viral competition study. The last two lanes are passage 11 analysis of duplicate passages of the competition study (each virus at MOI of 280 viral particles).

Figure 12 shows viral DNA analysis by *Hind* III digestion on high passage numbers for MRKAd5HIV-1gag in serum-containing media with collections made at specified times. The first lane shows the 1kb DNA size marker. The other lanes represent pre-plasmid control (digested with *Pac*1 and *Hind*III), MRKAd5HIV-1gag at P16, P19, and P21.

Figure 13 shows serum anti-p24 levels at 3 wks post i.m. immunization of balb/c mice (n=10) with varying doses of several Adgag constructs: (A) MRK Ad5 HIV-1 gag (through passage 5); (B) MRKAd5 hCMV-FLgag-bGHpA (E3-); (C) MRKAd5 hCMV-FLgag-SPA (E3+); (D) MRKAd5 mCMV-FLgag-bGHpA (E3+);

(E) research lot (293 cell-derived) of Ad5HIV-1 gag; and (F) clinical lot (Ad5gagFN0001) of Ad5HIV-1 gag. Reported are the geometric mean titers (GMT) for each cohort along with the standard error bars.

Figure 14 shows a restriction map of the pMRKAd5HIV-1gag vector.

5        Figures 15A-X illustrates the nucleotide sequence of the pMRKAd5HIV-1gag vector (SEQ ID NO:27.[coding] and SEQ ID NO:28 [non-coding]).

Figures 16A-B shows a schematic representation of DNA vaccine expression vectors V1Jns (A) and V1Jns-tPA (B), which are utilized for HIV-1 gag, pol and nef constructs in various DNA/viral vector combined modality regimens as disclosed  
10    herein.

Figures 17A-C shows the nucleotide (SEQ ID NO:3) and amino acid sequence (SEQ ID NO:4) of IA-Pol. Underlined codons and amino acids denote mutations, as listed in Table 1.

Figure 18 shows codon optimized nucleotide and amino acid sequences  
15    through the fusion junction of tPA-pol inact(opt) (contained within SEQ ID NOs: 7 and 8, respectively). The underlined portion represents the NH<sub>2</sub>-terminal region of IA-Pol.

Figures 19A-B show a nucleotide sequence comparison between wild type nef(jrfl) and codon optimized nef. The wild type nef gene from the jrfl isolate  
20    consists of 648 nucleotides capable of encoding a 216 amino acid polypeptide. WT, wild type sequence (SEQ ID NO:19); opt, codon-optimized sequence (contained within SEQ ID NO:1). The Nef amino acid sequence is shown in one-letter code (SEQ ID NO:2).

Figures 20A-C show nucleotide sequences at junctions between nef coding  
25    sequence and plasmid backbone of nef expression vectors V1Jns/nef (Figure 20A), V1Jns/nef(G2A,LLAA) (Figure 20B), V1Jns/tpanef (Figure 20C) and V1Jns/tpanef(LLAA) (Figure 20C, also). 5' and 3' flanking sequences of codon optimized nef or codon optimized nef mutant genes are indicated by bold/italic letters; nef and nef mutant coding sequences are indicated by plain letters. Also indicated (as  
30    underlined) are the restriction endonuclease sites involved in construction of respective nef expression vectors. V1Jns/tpanef and V1Jns/tpanef(LLAA) have identical sequences at the junctions.

Figure 21 shows a schematic presentation of nef and nef derivatives. Amino acid residues involved in Nef derivatives are presented. Glycine 2 and Leucine174  
35    and 175 are the sites involved in myristylation and dileucine motif, respectively. For both versions of the tpanef fusion genes, the putative leader peptide cleavage sites are

indicated with "\*", and a exogenous serine residue introduced during the construction of the mutants is underlined.

Figure 22 shows diagrammatically the construction of the pre-adenovirus plasmid construct, MRKAd5Pol.

5        Figure 23 shows diagrammatically the construction of the pre-adenovirus plasmid construct, MRKAd5Nef.

Figure 24 shows a comparison of clade B vs. clade C anti-gag T cell responses in clade B HIV-infected subjects.

10       Figure 25 shows a comparison of clade B vs. clade C anti-nef T cell responses in clade B HIV-infected subjects.

Figures 26A-AO illustrates the nucleotide sequence of the pMRKAd5HIV-1 pol adenoviral vector (SEQ ID NO:32 [coding] and SEQ ID NO:33 [non-coding]), comprising the coding region of the inactivated pol gene (SEQ ID NO3).

15       Figures 27A-AM illustrates the nucleotide sequence of the pMRKAd5HIV-1 nef adenoviral vector (SEQ ID NO:34 [coding] and SEQ ID NO:35 [non-coding]), comprising the coding region of the inactivated pol gene (SEQ ID NO13).

Figure 28 shows the stability of MRKAd5 vectors comprising various promoter fragments (hCMV or mCMV) and terminations signals (bGH or SPA) in E3(+) or E3(-) backbones.

20       Figures 29A and B shows the anion-exchange HPLC viral particle concentrations of the freeze-thaw recovered cell associated virus at the 24, 36, 48, and 60 hpi time points (Figure 29A) and the timcourse QPA supernatant titers (Figure 29B) for MRKAd5gag, MRKAd5pol and MRKAd5nef.

25       Figure 30 shows the nucleotide sequence (SEQ ID NO:36) and amino acid sequence (SEQ ID NO:37) comprising the open reading frame of a representative tPA-gag fusion for use in the DNA and/or adenoviral vaccine disclosed herein.

30       Figure 31 shows the intracellular  $\gamma$ IFN staining of PBMCs collected at week 10 (post DNA prime) and week 30 (post Ad boost). The cells were stimulated overnight in the presence or absence of the gag peptide pool. They were subsequently stained using fluorescence-tagged anti-CD3, anti-CD8, anti-CD4, and anti- $\gamma$ IFN monoclonal antibodies. Each plot shows all CD3+ T cells which were segregated in terms of positive staining for surface CD8 and  $\gamma$ IFN production. The numbers in the upper right and lower right quadrants of each plot are the percentages of CD3+ cells that were CD8+ $\gamma$ IFN+ and CD4+ $\gamma$ IFN+, respectively.

35       Figure 32 shows a comparison of single-modality adenovirus immunization with DNA + adjuvant prime/adenovirus boost immunization.

Figures 33A-B show the nucleotide sequence (SEQ ID NO: 38) of the open reading frame for the gag-IAPol fusion of Example 29.

Figures 34A-B show the protein sequence (SEQ ID NO:39) of the gag-IAPol fusion frame.

5

#### DETAILED DESCRIPTION OF THE INVENTION

A novel replication-defective, or "first generation," adenoviral vector suitable for use in gene therapy or nucleotide-based vaccine vectors is described. This vector is at least partially deleted in E1 and comprises a wildtype adenovirus *cis*-acting packaging region from about base pair 1 to between about base pair 342 (more preferably, 400) to about 458 (preferably, 1-450) and, preferably, 3511-3523 of a wild-type adenovirus sequence. It has been found that a vector of this description possesses enhanced growth characteristics, with approximately 5-10 fold greater amplification rates, and is more potent allowing lower doses of virus to be used to generate equivalent immunity. The vector, furthermore, generates a harvested recombinant adenovirus which shows greater cellular-mediated immune responses than replication-deficient vectors not comprising this region (basepairs 342-450). Adenoviral constructs derived from these vectors are, further, very stable genetically, particularly those comprising a transgene under the control of a hCMV promoter devoid of intron A. Viruses in accordance with this description were passaged continually and analyzed; see Example 12. Each virus analyzed maintained its correct genetic structure. Analysis was also carried out under propagation conditions similar to that performed in large scale production. Again, the vectors were found to possess enhanced genetic stability; see Figure 12. Following 21 passages, the viral DNA showed no evidence of rearrangement, and was highly reproducible from one production lot to the next. The outcome of all relevant tests indicate that the adenoviral vector is extremely well suited for large-scale production of recombinant, replication-deficient adenovirus, as shown herein with the data associated with Figure 28.

A preferred adenoviral vector in accordance with this description is a vector comprising basepairs 1-450, which is deleted in E3. This vector can accommodate up to approximately 7,500 base pairs of foreign DNA inserts (or exogenous genetic material). Another preferred vector is one retaining E3 which comprises basepairs 1-450. A preferred vector of this description is an E3+ vector comprising basepairs 1-450 and 3511-3523. This vector, when deleted of the region spanning basepairs 451-3510, can accommodate up to approximately, 4,850 base pairs of foreign DNA inserts

(or exogenous genetic material). The cloning capacities of the above vectors have been determined using 105% of the wildtype Ad5 sequence as the upper genome size limit.

Wildtype adenovirus serotype 5 is used as the basis for the specific basepair numbers provided throughout the specification. The wildtype adenovirus serotype 5 sequence is known and described in the art; *see*, Chroboczek *et al.*, 1992 *J. Virology* 186:280, which is hereby incorporated by reference. Accordingly, a particular embodiment of the instant invention is a vector based on the adenovirus serotype 5 sequence. One of skill in the art can readily identify the above regions in other adenovirus serotypes (e.g., serotypes 2, 4, 6, 12, 16, 17, 24, 31, 33, and 42), regions defined by basepairs corresponding to the above basepair positions given for adenovirus serotype 5. Accordingly, the instant invention encompasses all adenoviral vectors partially deleted in E1 comprising basepairs corresponding to 1-450 (particularly, 342-450) and, preferably, 3511-3523 of a wild-type adenovirus serotype 5 (Ad5) nucleic acid sequence. Particularly preferred embodiments of the instant invention are those derived from adenoviruses like Ad5 which are classified in subgroup C (e.g., Ad2).

Vectors in accordance with the instant invention are at least partially deleted in E1. Preferably the E1 region is completely deleted or inactivated. Most preferably, the region deleted of E1 is within basepairs 451-3510. It is to be noted that the extended 5' and 3' regions of the disclosed vectors are believed to effectively reduce the size of the E1 deletion of previous constructs without overlapping any part of the E1A/E1B gene present in the cell line used, i.e., the PER.C6<sup>®</sup> cell line transfected with base pairs 459-3510. Overlap of adenoviral sequences is avoided because of the possibility of recombination. One of ordinary skill in the art can certainly appreciate that the instant invention can, therefore, be modified if a different cell line transfected with a different segment of adenovirus DNA is utilized. For purposes of exemplification, a 5' region of base pairs 1 to up to 449 is more appropriate if a cell line is transfected with adenoviral sequence from base pairs 450-3510. This holds true as well in the consideration of segments 3' to the E1 deletion.

Preferred embodiments of the instant invention possess an intact E3 region (i.e., an E3 gene capable of encoding a functional E3). Alternate embodiments have a partially deleted E3, an inactivated E3 region, or a sequence completely deleted of E3. Applicants have found, in accordance with the instant invention, that virus comprising the E3 gene were able to amplify more rapidly compared with virus not comprising an E3 gene; see Figure 6 wherein a diagnostic CsCl band corresponding to the E3+ virus

tested (5,665 bp) was present in greater amount compared with the diagnostic band of 3,010 bp corresponding to the E3- virus. These results were obtained following a virus competition study involving mixing equal MOI ratio (1:1) of adenovectors both comprising the E3 gene and not comprising the E3 gene. This increased amplification capacity of the E3+ adenovectors was subsequently confirmed with growth studies; see Table 4A, wherein the E3+ virus exhibit amplification ratios of 470, 420 and 320 as compared with the 115 and 40-50 of the E3- constructs.

As stated above, vectors in accordance with the instant invention can accommodate up to approximately 4,850 base pairs of exogenous genetic material for an E3+ vector and approximately 7,500 base pairs for an E3- vector. Preferably, the insert brings the adenoviral vector as close as possible to a wild-type genomic size (e.g., for Ad5, 35,935 basepairs). It is well known that adenovirus amplifies best when they are close to their wild-type genomic size.

The genetic material can be inserted in an E1-parallel or an E1 anti-parallel orientation, as such is illustrated in Figure 7A, 7B, 7C and Figure 8A. Particularly preferred embodiments of the instant invention, have the insert in an E1-parallel orientation. Applicants have found, via competition experiments with plasmids containing transgenes in differing orientation (Figure 8A), that vector constructs with the foreign DNA insert in an E1-parallel orientation amplify better and actually out-compete E1-antiparallel-oriented transgenes. Viral DNA analysis of the mixtures at passage 3 and certainly at passage 6, showed a greater ratio of the virus carrying the transgene in the E1 parallel orientation as compared with the E1 anti-parallel version. By passage 10, the only viral species observed was the adenovector with the transgene in the E1 parallel orientation for both transgenes tested.

Adenoviral vectors in accordance with the instant invention are particularly well suited to effectuate expression of desired proteins, one example of which is an HIV protein, particularly an HIV full length gag protein. Exogenous genetic material encoding a protein of interest can exist in the form of an expression cassette. A gene expression cassette preferably comprises (a) a nucleic acid encoding a protein of interest; (b) a heterologous promoter operatively linked to the nucleic acid encoding the protein; and (c) a transcription terminator.

The transcriptional promoter is preferably recognized by an eukaryotic RNA polymerase. In a preferred embodiment, the promoter is a "strong" or "efficient" promoter. An example of a strong promoter is the immediate early human cytomegalovirus promoter (Chapman et al, 1991 *Nucl. Acids Res*19:3979-3986, which is incorporated by reference), preferably without intronic sequences. Most preferred

for use within the instant adenoviral vector is a human CMV promoter without intronic sequences, like intron A. Applicants have found that intron A, a portion of the human cytomegalovirus promoter (hCMV), constitutes a region of instability for adenoviral vectors. CMV without intron A has been found to effectuate (Examples 1-3) comparable expression capabilities *in vitro* when driving HIV gag expression and, furthermore, behaved equivalently to intron A-containing constructs in Balb/c mice *in vivo* with respect to their antibody and T-cell responses at both dosages of plasmid DNA tested (20 µg and 200 µg). Those skilled in the art will appreciate that any of a number of other known promoters, such as the strong immunoglobulin, or other eukaryotic gene promoters may also be used, including the EF1 alpha promoter, the murine CMV promoter, Rous sarcoma virus (RSV) promoter, SV40 early/late promoters and the beta-actin promoter.

In preferred embodiments, the promoter may also comprise a regulatable sequence such as the Tet operator sequence. This would be extremely useful, for example, in cases where the gene products are effecting a result other than that desired and repression is sought.

Preferred transcription termination sequences present within the gene expression cassette are the bovine growth hormone terminator/polyadenylation signal (bGHpA) and the short synthetic polyA signal (SPA) of 50 nucleotides in length, defined as follows: AATAAAAGATCTTTATTTTCATTAGATCTGTGTGTTGGT-TTTTGTGTG (SEQ ID NO:26).

The combination of the CMV promoter (devoid of the intron A region) with the BGH terminator is particularly preferred although other promoter/terminator combinations in the context of FG adenovirus may also be used.

Other embodiments incorporate a leader or signal peptide into the transgene. A preferred leader is that from the tissue-specific plasminogen activator protein, tPA. Examples include but are not limited to the various tPA-gag, tPA-pol and tPA-nef adenovirus-based vaccines disclosed throughout this specification.

In view of the improved adenovirus vectors described herein, an essential portion of the present invention are adenoviral-based HIV vaccines comprising said adenovirus backbones which may be administered to a mammalian host, preferably a human host, in either a prophylactic or therapeutic setting. The HIV vaccines of the present invention, whether administered alone or in combination regimens with other viral- or non-viral-based DNA vaccines, should elicit potent and broad cellular immune responses against HIV that will either lessen the likelihood of persistent virus infection and/or lead to the establishment of a clinically significant lowered virus load

subject to HIV infection or in combination with HAART therapy, mitigate the effects of previously established HIV infection (antiviral immunotherapy(ARI)). While any HIV antigen (e.g., gag, pol, nef, gp160, gp41, gp120, tat, rev, etc.) may be utilized in the herein described recombinant adenoviral vectors, preferred embodiments include the codon optimized p55 gag antigen (herein exemplified as MRKAd5gag), pol and nef. Sequences based on different Clades of HIV-1 are suitable for use in the instant invention, most preferred of which are Clade B and Clade C. Particularly preferred embodiments are those sequences (especially, codon-optimized sequences) based on consensus Clade B sequences. Preferred versions of the MRKAd5pol and MRKAd5nef series of adenoviral vaccines will encode modified versions of pol or nef, as discussed herein. Preferred embodiments of the MRKAd5HIV-1 vectors carrying HIV envelope genes and modifications thereof comprise the HIV codon-optimized *env* sequences of PCT International Applications PCT/US97/02294 and PCT/US97/10517, published August 28, 1997 (WO 97/31115) and December 24, 1997, respectively; both documents of which are hereby incorporated by reference.

A most preferred aspect of the instant invention is the disclosed use of the adenoviral vector described above to effectuate expression of HIV gag. Sequences for many genes of many HIV strains are publicly available in GENBANK and primary, field isolates of HIV are available from the National Institute of Allergy and Infectious Diseases (NIAID) which has contracted with Quality Biological (Gaithersburg, MD) to make these strains available. Strains are also available from the World Health Organization (WHO), Geneva Switzerland. It is preferred that the gag gene be from an HIV-1 strain (CAM-1; Myers et al, eds. "Human Retroviruses and AIDS: 1995, IIA3-IIA19, which is hereby incorporated by reference). This gene closely resembles the consensus amino acid sequence for the clade B (North American/European) sequence. Therefore, it is within the purview of the skilled artisan to choose an appropriate nucleotide sequence which encodes a specific HIV gag antigen, or immunologically relevant portion thereof. As shown in Example 25, a clade B or clade C based p55 gag antigen will potentially be useful on a global scale. As noted herein, the transgene of choice for insertion in to a DNA or MRKAd-based adenoviral vector of the present invention is a codon optimized version of p55 gag. Such a MRKAd5gag adenoviral vector is documented in Example 11 and is at least referred to herein as MRKAd5HIV-1gag. Of course, additional versions are contemplated, including but not limited to modifications such as promoter (e.g., mCMV for hCMV) and/or pA-terminations signal (SPA for bGH) switching, as well as generating MRK Ad5 backbones with or without deletion of the Ad5 E3 gene.

The present invention also relates a series of MRKAd5pol-based adenoviral vaccines which are shown herein to generate cellular immune responses subsequent to administration in mice and non-human primate studies. Several of the MRKAd5pol series are exemplified herein. One such adenoviral vector is referred to as

5 MRKAd5hCMV-inact opt pol(E3+), which comprises the MRKAd5 backbone, the hCMV promoter (no intron A), an inactivated pol transgene, and contains the Ad5 E3 gene in the adenoviral backbone. A second exemplified pre-adenovirus plasmid and concomitant virus is referred to as MRKAd5hCMV-inact opt pol(E3-), which is identical to the former adenoviral vector except that the E3 is deleted. Both

10 constructions contain a codon optimized, inactivated version of HIV-1 Pol, wherein at least the entire coding region is disclosed herein as SEQ ID NO:3 and the expressed protein is shown as SEQ ID NO:4 (see also Figure 17A-C and Table 1, which show targeted deletion for inactivated pol. This and other preferred codon optimized versions of HIV Pol as disclosed herein are essentially as described in U.S.

15 Application Serial No. 09/745,221, filed December 21, 2000 and PCT International Application PCT/US00/34724, also filed December 21, 2000, both documents which are hereby incorporated by reference. As disclosed in the above-mentioned documents, the open reading frame for these codon-optimized HIV-1 Pol-based DNA vaccines are represented by codon optimized DNA molecules encoding codon

20 optimized HIV-1 Pol (e.g. SEQ ID NO:2), codon optimized HIV-1 Pol fused to an amino terminal localized leader sequence (e.g. SEQ ID NO:6), and especially preferable, and exemplified by the MRKAd5-Pol construct in e.g., Example 19, biologically inactivated pol ("inact opt Pol"; e.g., SEQ ID NO:4) which is devoid of significant PR, RT, RNase or IN activity associated with wild type Pol. In addition,

25 a construct related to SEQ ID NO:4 is contemplated which contains a leader peptide at the amino terminal region of the IA Pol protein. A specific construct is ligated within an appropriate DNA plasmid vector containing regulatory regions operatively linked to the respective HIV-1 Pol coding region, with or without a nucleotide sequence encoding a functional leader peptide. To this end, various HIV-1 Pol constructs

30 disclosed herein relate to open reading frames for cloning to the enhanced first generation Ad vectors of the present invention (such a series of MRKAd5pol adenoviral vaccine vectors), including but not limited to wild type Pol (comprising the DNA molecule encoding WT opt Pol, as set forth in SEQ ID NO:2), tPA-opt WTPol, (comprising the DNA molecule encoding tPA Pol, as set forth in SEQ ID NO:6), inact

35 opt Pol (comprising the DNA molecule encoding IA Pol, as set forth in SEQ ID NO:4), and tPA-inact opt Pol, (comprising the DNA molecule encoding tPA-inact opt

Pol, as set forth in SEQ ID NO:8). The pol-based versions of enhanced first generation adenovirus vaccines elicit CTL and Th cellular immune responses upon administration to the host, including primates and especially humans. As noted in the above, an effect of the cellular immune-directed vaccines of the present invention should be a lower transmission rate to previously uninfected individuals and/or reduction in the levels of the viral loads within an infected individual, so as to prolong the asymptomatic phase of HIV-1 infection.

The present invention further relates to a series of MRKAd5nef-based adenoviral vaccines which, similar to HIV gag and pol antigens, generate cellular immune responses subsequent to administration in mice and non-human primate studies. The MRKAd5nef series are exemplified herein by utilizing the improved MRK adenoviral backbone in combination with modified versions of HIV nef. These exemplified MRKAd5nef vectors are as follows: (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+), which comprises the improved MRKAd5 backbone, a human CMV promoter an intact Ad5 E3 gene and a modified nef gene: (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+), which is the same as (1) above but substituting a murine CMV promoter for a human CMV promoter; and (3) MRKAd5mCMV-tpanef(LLAA) (E3+), which is the same as (2) except that the nef transgene is tpanef(LLAA). Codon optimized versions of HIV-1 Nef and HIV-1 Nef modifications are essentially as described in U.S. Application Serial No. 09/738,782, filed December 15, 2000 and PCT International Application PCT/US00/34162, also filed December 15, 2000, both documents which are hereby incorporated by reference. Particular embodiments of codon optimized Nef and Nef modifications relate to a DNA molecule encoding HIV-1 Nef from the HIV-1 jf1 isolate wherein the codons are optimized for expression in a mammalian system such as a human. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:9, while the expressed open reading frame is disclosed herein as SEQ ID NO:10. Another embodiment of Nef-based coding regions for use in the adenoviral vectors of the present invention comprise a codon optimized DNA molecule encoding a protein containing the human plasminogen activator (tpa) leader peptide fused with the NH<sub>2</sub>-terminus of the HIV-1 Nef polypeptide. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:11, while the expressed open reading frame is disclosed herein as SEQ ID NO:12. Another modified Nef optimized coding region relates to a DNA molecule encoding optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175, herein

described as opt nef (G2A, LLAA). The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:13, while the expressed open reading frame is disclosed herein as SEQ ID NO:14. MRKAd5nef vectors (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+) and (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+) contain this transgene. An additional embodiment relates to a DNA molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation site and dileucine motif have been deleted, as well as comprising a tPA leader peptide. This DNA molecule, opt tpanef (LLAA), comprises an open reading frame which encodes a Nef protein containing a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef (jfrl), wherein Leu-174 and Leu-175 are substituted with Ala-174 and Ala-175, herein referred to as opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, while the expressed open reading frame is disclosed herein as SEQ ID NO:16. The MRKAd5nef vector "MRKAd5mCMV-tpanef(LLAA) (E3+)" contains this transgene.

Along with the improved MRKAd5gag adenovirus vaccine vector described herein, generation of a MRKAd5pol and MRKAd5nef adenovirus vector provide for enhanced HIV vaccine capabilities. Namely, the generation of this trio of adenoviral vaccine vectors, all shown to generate effective cellular immune responses subsequent to host administration, provide for the ability to administer these vaccine candidates not only alone, but preferably as part of a divalent (i.e., gag and nef, gag and pol, or pol and nef components) or a trivalent vaccine (i.e., gag, pol and nef components). Therefore, a preferred aspect of the present invention are vaccine formulations and associated methods of administration and concomitant generation of host cellular immune responses associated with formulating three separate series of MRKAd5-based adenoviral vector vaccines. Of course, this MRKAd5 vaccine series based on distinct HIV antigens promotes expanded opportunities for formulation of a divalent or trivalent vaccine, or possibly administration of separate formulations of one or more monovalent or divalent formulations within a reasonable window of time. It is also within the scope of the present invention to embark on combined modality regimes which include multiple but distinct components from a specific antigen. An example, but certainly not a limitation, would be separate MRKAd5pol vectors, with one vaccine vector expressing wild type Pol (SEQ ID NO:2) and another MRKAd5pol vector expressing inactivated Pol (SEQ ID NO:6). Another example might be separate MRKAd5nef vectors, with one vaccine vector expressing the tPA/LLAA version of Nef (SEQ ID NO:16) and another MRKAd5nef vector expressing the G2A,LLAA modified version of Nef (SEQ ID NO:14). Therefore, the MRKAd5 adenoviral vectors of the present invention may be used in combination

with multiple, distinct HIV antigen classes. Each HIV antigen class is subject to sequence manipulation, thus providing for a multitude of potential vaccine combinations; and such combinations are within the scope of the present invention. The utilization of such combined modalities vaccine formulation and administration  
5 increase the probability of eliciting an even more potent cellular immune response when compared to inoculation with a single modality regimen.

The present invention also relates to application of a mono-, dual-, or tri-modality administration regime of the MRKAd5gag, pol and nef adenoviral vaccine series in a prime/boost vaccination schedule. This prime/boost schedule may include  
10 any reasonable combination of the MRKAd5gag, pol and nef adenoviral vaccine series disclosed herein. In addition, a prime/boost regime may also involve other viral and/or non-viral DNA vaccines. A preferable addition to an adenoviral vaccine vector regime includes but is not limited to plasmid DNA vaccines, especially DNA plasmid vaccines that contain at least one of the codon optimized gag, pol and nef  
15 constructions, as disclosed herein.

Therefore, one aspect of this invention is the administration of the adenoviral vector containing the optimized gag gene in a prime/boost regimen in conjunction with a plasmid DNA encoding gag. To distinguish this plasmid from the adenoviral-containing shuttle plasmids used in the construction of an adenovirus vector, this  
20 plasmid will be referred to as a "vaccine plasmid" or "DNA plasmid vaccine". Preferred vaccine plasmids for use in this administration protocol are disclosed in pending U.S. patent application 09/017,981, filed February 3, 1998 and WO98/34640, published August 13, 1998, both of which are hereby incorporated by reference. Briefly, the preferred vaccine plasmid is designated V1Jns-FLgag, which expresses  
25 the same codon-optimized gag gene as the adenoviral vectors of this invention (see Figure 2 for the nucleotide sequence of the exemplified optimized codon version of full length p55 gag). The vaccine plasmid backbone, designated V1Jns contains the CMV immediate-early (IE) promoter and intron A, a bovine growth hormone-derived polyadenylation and transcription termination sequence as the gene expression  
30 regulatory elements, and a minimal pUC backbone; see Montgomery *et al.*, 1993, *DNA Cell Biol.* 12:777-783. The pUC sequence permits high levels of plasmid production in *E. coli* and has a neomycin resistance gene in place of an ampicillin resistance gene to provide selected growth in the presence of kanamycin. Alternatively, a vaccine plasmid which has the CMV promoter deleted of intron A can  
35 be used. Those of skill in the art will recognize that alternative vaccine plasmid

vectors may be easily substituted for these specific constructs, and this invention specifically envisions use of such alternative plasmid DNA vaccine vectors.

Another aspect of the present invention is a prime/boost regimen which includes a vaccine plasmid which encodes an HIV pol antigen, preferably a codon optimized form of pol and also preferably a vaccine plasmid which comprises a  
5 nucleotide sequence which encodes a Pol antigen selected from the group of Pol antigens as shown in SEQ ID NOs: 2, 4, 6 and 8. The variety of potential DNA plasmid vaccines which encode various biologically active forms of HIV-1 Pol, wherein administration, intracellular delivery and expression of the HIV-1 Pol gene of  
10 interest elicits a host CTL and Th response. The preferred synthetic DNA molecules of the present invention encode codon optimized wild type Pol (without Pro activity) and various codon optimized inactivated HIV-1 Pol proteins. The HIV-1 *pol* open reading disclosed herein are especially preferred for pharmaceutical uses, especially for human administration as delivered via a recombinant adenoviral vaccine,  
15 especially an enhanced first generation recombinant adenoviral vaccine as described herein. Several embodiments of this portion of the invention are provided in detail below, namely DNA molecules which comprise a HIV-1 pol open reading frame, whether encoding full length pol or a modification or fusion as described herein, wherein the codon usage has been optimized for expression in a mammal, especially a  
20 human. Again, these DNA sequences are positioned appropriately within a recombinant adenoviral vector, such as the exemplified recombinant adenoviral vector described herein, so as to promote expression of the respective HIV-1 Pol gene of interest, and subsequent to administration, elicit a host CTL and Th response. Again, these preferred, but in no way limiting, pol genes are as disclosed herein and  
25 essentially as described in U.S. Application Serial No. 09/745,221, filed December 21, 2000 and PCT International Application PCT/US00/34724, also filed December 21, 2000, both documents which are hereby incorporated by reference.

A third series of vaccine plasmids which are useful in a combined modality and/or prime/boost regimen are vaccine plasmids which encode an HIV nef antigen or  
30 biologically and/or immunologically relevant modification thereof. As noted elsewhere, preferred vaccine plasmids contain a codon optimized form of nef and also preferably comprise a nucleotide sequence which encodes a Nef antigen selected from the group of Nef antigens as shown in SEQ ID NOs: 10, 12, 14 and 16. These preferred nef coding regions are disclosed herein, as well as being described in U.S.  
35 Application Serial No. 09/738,782, filed December 15, 2000 and PCT International

Application PCT/US00/34162, also filed December 15, 2000, both documents which are hereby incorporated by reference.

Therefore, the adenoviral vaccines and plasmid DNA vaccines of this invention may be administered alone, or may be part of a prime and boost administration regimen. A mixed modality priming and booster inoculation scheme will result in an enhanced immune response, particularly if pre-existing anti-vector immune responses are present. This one aspect of this invention is a method of priming a subject with the plasmid vaccine by administering the plasmid vaccine at least one time, allowing a predetermined length of time to pass, and then boosting by administering the adenoviral vaccine. Multiple primings typically, 1-4, are usually employed, although more may be used. The length of time between priming and boost may typically vary from about four months to a year, but other time frames may be used. In experiments with rhesus monkeys, the animals were primed four times with plasmid vaccines, then were boosted 4 months later with the adenoviral vaccine. Their cellular immune response was notably higher than that of animals which had only received adenoviral vaccine. The use of a priming regimen may be particularly preferred in situations where a person has a pre-existing anti-adenovirus immune response.

Furthermore and in the alternative, multiple HIV-1 viral antigens, such as the MRKAd5 adenoviral vaccines disclosed herein, may be ligated into a proper shuttle plasmid for generation of a pre-adenoviral plasmid comprising multiple open reading frames. For example a trivalent vector may comprise a gag-pol-nef fusion, in either a E3(-) or E3(+) background, preferably a E3 deleted backbone, or possibly a "2+1" divalent vaccine, such as a gag-pol fusion (i.e., codon optimized p55 gag and inactivated optimized pol; Example 29 and Table 25) within the same MRKAd5 backbone, with each open reading frame being operatively linked to a distinct promoter and transcription termination sequence. Alternatively, the two open reading frames may be operatively linked to a single promoter, with the open reading frames operatively linked by an internal ribosome entry sequence (IRES), as disclosed in International Publication No. WO 95/24485, which is hereby incorporated by reference. Figure 9 shows that the use of multiple promoters and termination sequences provide for similar growth properties, while Figure 28 shows that these MRKAd5gag-based vectors are also stable at least through passage 21. In the absence of the use of IRES-based technology, it is preferred that a distinct promoter be used to support each respective open reading frame, so as to best preserve vector stability. As examples, and certainly not as limitations, potential multiple transgene vaccines may

include a three transgene vector such as hCMV-gagpol-bGHpA + mCMV-nef-SPA in an E3 deleted backbone or hCMV-gagpol-bGHpA + mCMV-nef-SPA(E3+).

Potential "2+1" divalent vaccines of the present invention might be a hCMV-gag-bGHpA + mCMV-nef-SPA in an E3+ backbone (vector #1) in combination with  
5 hCMV-pol-bGHpA in an E3+ backbone (vector #2), with all transgenes in the E1 parallel orientation. Fusion constructs other than the gag-pol fusion described above are also suitable for use in various divalent vaccine strategies and can be composed of any two HIV antigens fused to one another (*e.g.*, nef-pol and gag-nef). These  
10 adenoviral compositions are, as above, preferably delivered along with an adenoviral composition comprising an additional HIV antigen in order to diversify the immune response generated upon administration. Therefore, a multivalent vaccine delivered in a single, or possible second, adenoviral vector is certainly contemplated as part of the present invention. Again, this mode of administration is another example of  
15 whereby an efficacious adenovirus-based HIV-1 vaccine may be administered via a combined modality regime. It is important to note, however, that in terms of deciding on an insert for the disclosed adenoviral vectors, due consideration must be dedicated to the effective packaging limitations of the adenovirus vehicle. Adenovirus has been shown to exhibit an upper cloning capacity limit of approximately 105% of the wildtype Ad5 sequence.

20 Regardless of the gene chosen for expression, it is preferred that the sequence be "optimized" for expression in a human cellular environment. A "triplet" codon of four possible nucleotide bases can exist in 64 variant forms. That these forms provide the message for only 20 different amino acids (as well as transcription initiation and termination) means that some amino acids can be coded for by more than one codon.  
25 Indeed, some amino acids have as many as six "redundant", alternative codons while some others have a single, required codon. For reasons not completely understood, alternative codons are not at all uniformly present in the endogenous DNA of differing types of cells and there appears to exist variable natural hierarchy or "preference" for certain codons in certain types of cells. As one example, the amino  
30 acid leucine is specified by any of six DNA codons including CTA, CTC, CTG, CTT, TTA, and TTG (which correspond, respectively, to the mRNA codons, CUA, CUC, CUG, CUU, UUA and UUG). Exhaustive analysis of genome codon frequencies for microorganisms has revealed endogenous DNA of *E. coli* most commonly contains the CTG leucine-specifying codon, while the DNA of yeasts and slime molds most  
35 commonly includes a TTA leucine-specifying codon. In view of this hierarchy, it is generally held that the likelihood of obtaining high levels of expression of a leucine-

rich polypeptide by an *E. coli* host will depend to some extent on the frequency of codon use. For example, a gene rich in TTA codons will in all probability be poorly expressed in *E. coli*, whereas a CTG rich gene will probably highly express the polypeptide. Similarly, when yeast cells are the projected transformation host cells for expression of a leucine-rich polypeptide, a preferred codon for use in an inserted DNA would be TTA.

The implications of codon preference phenomena on recombinant DNA techniques are manifest, and the phenomenon may serve to explain many prior failures to achieve high expression levels of exogenous genes in successfully transformed host organisms--a less "preferred" codon may be repeatedly present in the inserted gene and the host cell machinery for expression may not operate as efficiently. This phenomenon suggests that synthetic genes which have been designed to include a projected host cell's preferred codons provide a preferred form of foreign genetic material for practice of recombinant DNA techniques. Thus, one aspect of this invention is an adenovirus vector or adenovirus vector in some combination with a vaccine plasmid where both specifically include a gene which is codon optimized for expression in a human cellular environment. As noted herein, a preferred gene for use in the instant invention is a codon-optimized HIV gene and, particularly, HIV gag, pol or nef.

Adenoviral vectors in accordance with the instant invention can be constructed using known techniques, such as those reviewed in Hitt et al, 1997 "Human Adenovirus Vectors for Gene Transfer into Mammalian Cells" *Advances in Pharmacology* 40:137-206, which is hereby incorporated by reference.

In constructing the adenoviral vectors of this invention, it is often convenient to insert them into a plasmid or shuttle vector. These techniques are known and described in Hitt et al., *supra*. This invention specifically includes both the adenovirus and the adenovirus when inserted into a shuttle plasmid.

Preferred shuttle vectors contain an adenoviral portion and a plasmid portion. The adenoviral portion is essentially the same as the adenovirus vector discussed *supra*, containing adenoviral sequences (with non-functional or deleted E1 and E3 regions) and the gene expression cassette, flanked by convenient restriction sites. The plasmid portion of the shuttle vector often contains an antibiotic resistance marker under transcriptional control of a prokaryotic promoter so that expression of the antibiotic does not occur in eukaryotic cells. Ampicillin resistance genes, neomycin resistance genes and other pharmaceutically acceptable antibiotic resistance markers may be used. To aid in the high level production of the polynucleotide by

fermentation in prokaryotic organisms, it is advantageous for the shuttle vector to contain a prokaryotic origin of replication and be of high copy number. A number of commercially available prokaryotic cloning vectors provide these benefits. It is desirable to remove non-essential DNA sequences. It is also desirable that the vectors not be able to replicate in eukaryotic cells. This minimizes the risk of integration of polynucleotide vaccine sequences into the recipients' genome. Tissue-specific promoters or enhancers may be used whenever it is desirable to limit expression of the polynucleotide to a particular tissue type.

In one embodiment of this invention, the pre-plasmids (e.g., pMRKAd5pol, pMRKAd5nef and pMRKAd5gag) were generated by homologous recombination using the MRKHVE3 (and MRKHVO for the E3- version) backbones and the appropriate shuttle vector, as shown for pMRKAd5pol in Figure 22 and for pMRKAd5nef in Figure 23. The plasmid in linear form is capable of replication after entering the PER.C6<sup>®</sup> cells and virus is produced. The infected cells and media were harvested after viral replication was complete.

Viral vectors can be propagated in various E1 complementing cell lines, including the known cell lines 293 and PER.C6<sup>®</sup>. Both these cell lines express the adenoviral E1 gene product. PER.C6<sup>®</sup> is described in WO 97/00326 (published January 3, 1997) and issued U.S. Patent No. 6,033,908, both of which are hereby incorporated by reference. It is a primary human retinoblast cell line transduced with an E1 gene segment that complements the production of replication deficient (FG) adenovirus, but is designed to prevent generation of replication competent adenovirus by homologous recombination. Cells of particular interest have been stably transformed with a transgene that encodes the AD5E1A and E1B gene, like PER.C6<sup>®</sup>, from 459 bp to 3510 bp inclusive. 293 cells are described in Graham et al., 1977 *J. Gen. Virol* 36:59-72, which is hereby incorporated by reference. As stated above, consideration must be given to the adenoviral sequences present in the complementing cell line used. It is important that the sequences not overlap with that present in the vector if the possibility of recombination is to be minimized.

It has been found that vectors generated in accordance with the above description are more effective in inducing an immune response and, thus, constitute very promising vaccine candidates. More particularly, it has been found that first generation adenoviral vectors in accordance with the above description carrying a codon-optimized HIV gag gene, regulated with a strong heterologous promoter can be used as human anti-HIV vaccines, and are capable of inducing immune responses.

Standard techniques of molecular biology for preparing and purifying DNA constructs enable the preparation of the DNA immunogens of this invention.

A vaccine composition comprising an adenoviral vector in accordance with the instant invention may contain physiologically acceptable components, such as  
5 buffer, normal saline or phosphate buffered saline, sucrose, other salts and polysorbate. One preferred formulation has: 2.5-10 mM TRIS buffer, preferably about 5 mM TRIS buffer; 25-100 mM NaCl, preferably about 75 mM NaCl; 2.5-10% sucrose, preferably about 5% sucrose; 0.01 -2 mM  $MgCl_2$ ; and 0.001%-0.01% polysorbate 80 (plant derived). The pH should range from about 7.0-9.0, preferably  
10 about 8.0. One skilled in the art will appreciate that other conventional vaccine excipients may also be used it make the formulation. The preferred formulation contains 5mM TRIS, 75 mM NaCl, 5% sucrose, 1mM  $MgCl_2$ , 0.005% polysorbate 80 at pH 8.0 This has a pH and divalent cation composition which is near the optimum for Ad5 stability and minimizes the potential for adsorption of virus to a glass surface.  
15 It does not cause tissue irritation upon intramuscular injection. It is preferably frozen until use.

The amount of adenoviral particles in the vaccine composition to be introduced into a vaccine recipient will depend on the strength of the transcriptional and translational promoters used and on the immunogenicity of the expressed gene  
20 product. In general, an immunologically or prophylactically effective dose of  $1 \times 10^7$  to  $1 \times 10^{12}$  particles and preferably about  $1 \times 10^{10}$  to  $1 \times 10^{11}$  particles is administered directly into muscle tissue. Subcutaneous injection, intradermal introduction, impression through the skin, and other modes of administration such as intraperitoneal, intravenous, or inhalation delivery are also contemplated. It is also  
25 contemplated that booster vaccinations are to be provided. Following vaccination with HIV adenoviral vector, boosting with a subsequent HIV adenoviral vector and/or plasmid may be desirable. Parenteral administration, such as intravenous, intramuscular, subcutaneous or other means of administration of interleukin-12 protein, concurrently with or subsequent to parenteral introduction of the vaccine  
30 compositions of this invention is also advantageous.

The adenoviral vector and/or vaccine plasmids of this invention polynucleotide may be unassociated with any proteins, adjuvants or other agents which impact on the recipients' immune system. In this case, it is desirable for the vector to be in a physiologically acceptable solution, such as, but not limited to, sterile  
35 saline or sterile buffered saline. Alternatively, the vector may be associated with an adjuvant known in the art to boost immune responses (i.e., a "biologically effective"

adjuvant), such as a protein or other carrier. Vaccine plasmids of this invention may, for instance, be delivered in saline (e.g., PBS) with or without an adjuvant. Preferred adjuvants are Alum or CRL1005 Block Copolymer. Agents which assist in the cellular uptake of DNA, such as, but not limited to, calcium ions, may also be used to advantage. These agents are generally referred to herein as transfection facilitating reagents and pharmaceutically acceptable carriers. Techniques for coating microprojectiles coated with polynucleotide are known in the art and are also useful in connection with this invention.

This invention also includes a prime and boost regimen wherein a first adenoviral vector is administered, then a booster dose is given. The booster dose may be repeated at selected time intervals. Alternatively, a preferred inoculation scheme comprises priming with a first adenovirus serotype and then boosting with a second adenovirus serotype. More preferably, the inoculation scheme comprises priming with a first adenovirus serotype and then boosting with a second adenovirus serotype, wherein the first and second adenovirus serotypes are classified within separate subgroups of adenoviruses. The above prime/boost schemes are particularly preferred in those situations where a preexisting immunity is identified to the adenoviral vector of choice. In this type of scheme, the individual or population of individuals is primed with an adenovirus of a serotype other than that to which the preexisting immunity is identified. This enables the first adenovirus to effectuate sufficient expression of the transgene while evading existing immunity to the second adenovirus (the boosting adenovirus) and, further, allows for the subsequent delivery of the transgene via the boosting adenovirus to be more effective. Adenovirus serotype 5 is one example of a virus to which such a scheme might be desirable. In accordance with this invention, therefore, one might decide to prime with a non-group C adenovirus (e.g., Ad12, a group A adenovirus, Ad24, a group D adenovirus, or Ad35, a group B adenovirus) to evade anti-Ad5 immunity and then boost with Ad5, a group C adenovirus. Another preferred embodiment involves administration of a different adenovirus (including non-human adenovirus) vaccine followed by administration of the adenoviral vaccines disclosed. In the alternative, a viral antigen of interest can be first delivered via a viral vaccine other than an adenovirus-based vaccine, and then followed with the adenoviral vaccine disclosed. Alternative viral vaccines include but are not limited to pox virus and venezuelan equine encephalitis virus.

A large body of human and animal data supports the importance of cellular immune responses, especially CTL in controlling (or eliminating) HIV infection. In humans, very high levels of CTL develop following primary infection and correlate

with the control of viremia. Several small groups of individuals have been described who are repeatedly exposed to HIV by remain uninfected; CTL has been noted in several of these cohorts. In the SIV model of HIV infection, CTL similarly develops following primary infection, and it has been demonstrated that addition of anti-CD8 monoclonal antibody abrogated this control of infection and leads to disease progression. This invention uses adenoviral vaccines alone or in combination with plasmid vaccines to induce CTL.

The following non-limiting Examples are presented to better illustrate the invention.

#### EXAMPLE 1

##### Removal of the Intron A Portion of the hCMV Promoter

GMP grade pVII<sub>ns</sub>HIVgag was used as the starting material to amplify the hCMV promoter. PVI<sub>ns</sub>HIVgag is a plasmid comprising the CMV immediate-early (IE) promoter and intron A, a full-length codon-optimized HIV gag gene, a bovine growth hormone-derived polyadenylation and transcriptional termination sequence, and a minimal pUC backbone; see Montgomery *et al.*, *supra* for a description of the plasmid backbone. The amplification was performed with primers suitably positioned to flank the hCMV promoter. A 5' primer was placed upstream of the *MscI* site of the hCMV promoter and a 3' primer (designed to contain the *Bgl*III recognition sequence) was placed 3' of the hCMV promoter. The resulting PCR product (using high fidelity *Taq* polymerase) which encompassed the entire hCMV promoter (minus intron A) was cloned into TOPO PCR blunt vector and then removed by double digestion with *MscI* and *Bgl*III. This fragment was then cloned back into the original GMP grade pVI<sub>ns</sub>HIVgag plasmid from which the original promoter, intron A, and the gag gene were removed following *MscI* and *Bgl*III digestion. This ligation reaction resulted in the construction of a hCMV promoter (minus intron A) + bGHpA expression cassette within the original pVI<sub>ns</sub>HIVgag vector backbone. This vector is designated pVII<sub>ns</sub>CMV(no intron).

The FLgag gene was excised from pVI<sub>ns</sub>HIVgag using *Bgl*III digestion and the 1,526 bp gene was gel purified and cloned into pVI<sub>ns</sub>CMV(no intron) at the *Bgl*III site. Colonies were screened using *Sma*I restriction enzymes to identify clones that carried the FLgag gene in the correct orientation. This plasmid, designated pVI<sub>ns</sub>CMV(no intron)-FLgag-bGHpA, was fully sequenced to confirm sequence integrity.

Two additional transgenes were also constructed. The plasmid, pV1JnsCMV(no intron)-FLgag-SPA, is identical to pV1JnsCMV(no intron)-FLgag-bGHpA except that the bovine growth hormone polyadenylation signal has been replaced with a short synthetic polyA signal (SPA) of 50 nucleotides in length. The sequence of the SPA is as shown, with the essential components (poly(A) site, (GT)<sub>n</sub>, and (T)<sub>n</sub>; respectively) underlined:

AATAAAAGATCTTTATTTTCATTAGATCTGTGTG TTGGTTTTTTGTGTG  
(SEQ ID NO:18).

The plasmid, pV1Jns-mCMV-FLgag-bGHpA, is identical to the pV1JnsCMV(no intron)-FLgag-bGHpA except that the hCMV promoter has been removed and replaced with the murine CMV (mCMV) promoter.

Figure 3 diagrammatically shows the new transgene constructs in comparison with the original transgene.

## EXAMPLE 2

### Gag Expression Assay for Modified Gag Transgenes

Gag Elisa was performed on culture supernatants obtained from transient tissue culture transfection experiments in which the two new hCMV-containing plasmid constructs, pV1JnsCMV(no intron)-FLgag-bGHpA and pV1JnsCMV(no intron)-FLgag-SPA, both devoid of intron A, were compared to pV1JnsHIVgag which, as noted above possesses the intron A as part of the hCMV promoter. Table 2 below shows the *in vitro* gag expression data of the new gag plasmids compared with the GMP grade original plasmid. The results displayed in Table 2 show that both of the new hCMV gag plasmid constructs have expression capacities comparable to the original plasmid construct which contains the intron A portion of the hCMV promoter.

Table 2: *In vitro* DNA transfection of original and new plasmid HIV-1 gag constructs.

Plasmid	$\mu\text{g gag}/10^6 \text{ COS cells}/5\mu\text{g DNA}/48 \text{ hr}$
HIVFL-gagPR9901 <sup>a</sup>	10.8
PV1Jns-hCMV-FLgag-bGHpA <sup>b</sup>	16.6
pV1Jns-hCMV-FLgag-SPA <sup>b,c</sup>	12.0

<sup>a</sup> GMP grade pV1Jns-hCMVintronA-FLgag-bGHpA.

5 <sup>b</sup> New plasmid constructions that have the intron A portion removed from the hCMV promoter.

<sup>c</sup> In this construct the bGH terminator has been replaced with the short synthetic polyadenylation signal (SPA)

10

### EXAMPLE 3

#### Rodent (Balb/c) Study for Modified gag Transgenes

A rodent study was performed on the two new plasmid constructs described above – pV1JnsCMV(no intron)-FLgag-bGHpA and pV1JnsCMV(no intron)-FLgag-SPA - in order to compare them with the construct described above  
 15 possessing the intron A portion of the CMV promoter, pV1JnsHIVgag. Gag antibody and Elispot responses (described in PCT International Application No. PCT/US00/18332 (WO 01/02607) filed July 3, 2000, claiming priority to U.S. Provisional Application Serial No. 60/142,631, filed July 6, 1999 and U.S. Application Serial No. 60/148,981, filed August 13, 1999, all three applications which  
 20 are hereby incorporated by reference) were measured. The results displayed in Table 3 below, show that the new plasmid constructs behaved equivalently to the original construct in Balb/c mice with respect to their antibody and T-cell responses at both dosages of plasmid DNA tested, 20  $\mu\text{g}$  and 200  $\mu\text{g}$ .

## EXAMPLE 4

Table 3: HIV191: Immunogenicity of V1Jns-gag under different promoter and termination control elements.

DNA <sup>a</sup> Promoter/terminator	Dose, ug <sup>b</sup>	Anti-p24 Titers (3 Wk PD1) <sup>c</sup>			SFC/10 <sup>6</sup> Cells (4 Wk PD1) <sup>d</sup>		
		GMT	+SE	-SE	Media	gag197-205	p24
HIVFL-gagPR9901 (GMP grade)	200	12800	4652	3412	2(2)	129(19)	30(11)
	20	5572	1574	1227	0	56(9)	25(6)
pV1Jns-hCMV- FL-gag-bGHpA	200	11143	2831	2257	0	98(5)	12(6)
	20	7352	2808	2032	0	73(9)	11(6)
pV1Jns-hCMV- FL-gag-SPA	200	16890	5815	4326	1(1)	94(4)	26(7)
	20	5971	5361	2825	0	85(17)	38(10)
Naïve	0	123	50	36	0	0	0

<sup>a</sup>in PBS<sup>b</sup>i.m. Injections into both quads, 50 µL per quad<sup>c</sup>n=10; GMT, geometric mean titer; SE, standard. error<sup>d</sup>n=5, pooled spleens; mean of triplicate wells and standard. deviation. in parentheses;

## Construction of the Modified Shuttle Vector -"MRKpdeIE1 Shuttle"

The modifications to the original Ad5 shuttle vector (pdeIE1sp1A; a vector comprising Ad5 sequences from basepairs 1-341 and 3524-5798, with a multiple cloning region between nucleotides 341 and 3524 of Ad5, included the following three manipulations carried out in sequential cloning steps as follows:

(1) The left ITR region was extended to include the *Pac*1 site at the junction between the vector backbone and the adenovirus left ITR sequences. This allow for easier manipulations using the bacterial homologous recombination system.

(2) The packaging region was extended to include sequences of the wild-type (WT) adenovirus from 342 bp to 450 bp inclusive.

(3) The area downstream of pIX was extended 13 nucleotides (i.e., nucleotides 3511-3523 inclusive).

These modifications (Figure 4) effectively reduced the size of the E1 deletion without overlapping with any part of the E1A/E1B gene present in the transformed PER.C6<sup>®</sup> cell line. All manipulations were performed by modifying the Ad shuttle vector pdeIE1sp1A.

Once the modifications were made to the shuttle vector, the changes were incorporated into the original Ad5 adenovector backbones (pAdHVO and pAdHVE3) by bacterial homologous recombination using *E. coli* BJ5183 chemically competent cells.

## EXAMPLE 5

Construction of Modified Adenovector Backbones (E3+ and E3-)

The original adenovectors pAdHVO (comprising all Ad5 sequences except those nucleotides encompassing the E1 and E3 regions ) and pAdHVE3 (comprising all Ad5 sequences except those nucleotides encompassing the E1 region), were each reconstructed so that they contained the modifications to the E1 region. This was accomplished by digesting the newly modified shuttle vector (MRKpdeIE1 shuttle) with *Pac*I and *Bst*Z1101 and isolating the 2,734 bp fragment which corresponds to the adenovirus sequence. This fragment was co-transformed with DNA from either *Cla*I linearized pAdHVO (E3- adenovector) or *Cla*I linearized pAdHVE3 (E3+adenovector) into *E. coli* BJ5183 competent cells. At least two colonies from each transformation were selected and grown in Terrific™ broth for 6-8 hours until turbidity was reached. DNA was extracted from each cell pellet and then transformed into *E. coli* XL1 competent cells. One colony from each transformation was selected and grown for plasmid DNA purification. The plasmid was analyzed by restriction digestions to identify correct clones. The modified adenovectors were designated MRKpAdHVO (E3- plasmid) and MRKpAdHVE3 (E3+ plasmid). Virus from these new adenovectors (MRKHVO and MRKHVE3, respectively) as well as the old version of the adenovectors were generated in the PER.C6® cell lines to accommodate the following series of viral competition experiments. In addition, the multiple cloning site of the original shuttle vector contained *Cla*I, *Bam*HI, *Xho*I, *Eco*RV, *Hind*III, *Sal*I, and *Bgl*II sites. This MCS was replaced with a new MCS containing *Not*I, *Cla*I, *Eco*RV and *Asc*I sites. This new MCS has been transferred to the MRKpAdHVO and MRKpAdHVE3 pre-plasmids along with the modification made to the packaging region and pIX gene.

## EXAMPLE 6

Analysis of the Effect of the Packaging Signal Extension

To study the effects of the modifications made to the E1 deletion region, the viruses obtained from the original backbone (pAdHVE3) and the new backbone (MRKpAdHVE3) were mixed together in equal MOI ratios (1:1 and 5:5) and passaged through several rounds; see Figure 5, Expt.#1. Both of the viruses in the experiment contained the E3 gene intact and did not contain a transgene. The only difference between the two viruses was within the region of the E1 deletion. Following the coinfection of the viruses at P1 (passage 1), the mixtures were propagated through an additional 4 passages at which time the cells were harvested

and the virus extracted and purified by CsCl banding. The viral DNA was extracted and digested with *HindIII* and the digestion products were then radioactively labeled. For the controls, the respective pre-plasmids (pAdHVE3 ("OLD E3+"); MRKpAdHVE3 ("NEW E3+")) were also digested with *HindIII* (and *PacI* to remove the vector backbone) and subsequently labeled with [<sup>33</sup>P]dATP. The radioactively labeled digestion products were subjected to gel electrophoresis and the gel was dried down onto Whatman paper before being exposed to autoradiographic film. Figure 6 clearly shows that the new adenovirus which has the addition made to the packaging signal region has a growth advantage compared with the original adenovirus. In the experiments performed (at either ratio tested), only the digestion bands pertaining to the newly modified virus were present. The diagnostic band of size 3,206 (from the new virus) was clearly present. However, there was no evidence of the diagnostic band of size 2,737 bp expected from the original virus.

#### EXAMPLE 7

##### Analysis of the Effect of the E3 Gene

The second set of the virus competition study involved mixing equal MOI ratio (1:1) of the newly modified viruses, that obtained from MRKpAdHVO and MRKpAdHVE3 (Figure 5, Expt. #2). In this set, both viruses had the new modifications made to the E1 deletion. The first virus (that from MRKpAdHVO) does not contain an E3 gene. The second virus (that from MRKpAdHVE3) does contain the E3 gene. Neither of the viruses contain a transgene. Following co-infection of the viruses, the mixtures were propagated through an additional 4 passages at which time the cells were harvested and the total virus extracted and purified by CsCl banding. The viral DNA was extracted and digested with *HindIII* and the digestion products were then radioactively labeled. For the controls, the respective pre-plasmids MRKpAdHVO ("NEW E3-"); MRKpAdHVE3 ("NEW E3+") were also digested with *HindIII* (and *PacI* to remove the vector backbone) and then labeled with [<sup>33</sup>P]dATP. The radioactively labeled digestion products were subjected to gel electrophoresis and the gel was dried down onto Whatman paper before being exposed to autoradiographic film. Figure 6 shows the results of the viral DNA analysis of the E3+ virus and E3- virus mixing experiment. The diagnostic band corresponding to the E3+ virus (5,665 bp) was present in greater amount compared with the diagnostic band of 3,010 bp corresponding to the E3- virus. This indicates that the virus that contains the E3 gene is able to amplify more rapidly

compared with the virus that does not contain an E3 gene. This increased amplification capacity has been confirmed by growth studies; see Table 4 below.

#### EXAMPLE 8

5     Construction of the new shuttle vector containing modified gag transgene –  
          "MRKpdeIE1-CMV(no intron)-FLgag-bGHpA"

10     The modified plasmid pV1JnsCMV(no intron)-FLgag-bGHpA was digested with *MscI* overnight and then digested with *SfiI* for 2 hours at 50°C. The DNA was then treated with Mungbean nuclease for 30 mins at 30°C. The DNA mixture was  
15     desalted using the Qiaex II kit and then Klenow treated for 30 mins at 37°C to fully blunt the ends of the transgene fragment. The 2,559 bp transgene fragment was then gel purified. The modified shuttle vector (MRKpdeIE1 shuttle) was linearized by digestion with *EcoRV*, treated with calf intestinal phosphatase and the resulting 6,479 bp fragment was then gel purified. The two purified fragments were then ligated  
20     together and several dozen clones were screened to check for insertion of the transgene within the shuttle vector. Diagnostic restriction digestion was performed to identify those clones carrying the transgene in the E1 parallel and E1 anti-parallel orientation. This strategy was followed to clone in the other gag transgenes in the MRKpdeIE1 shuttle vector.

#### EXAMPLE 9

Construction of the MRK FG Adenovectors

          The shuttle vector containing the HIV-1 gag transgene in the E1 parallel orientation, MRKpdeIE1-CMV(no intron)-FLgag-bGHpA, was digested with *PacI*.  
25     The reaction mixture was digested with *BsfZ171*. The 5,291 bp fragment was purified by gel extraction. The MRKpAdHVE3 plasmid was digested with *ClaI* overnight at 37°C and gel purified. About 100 ng of the 5,290 bp shuttle +transgene fragment and ~100 ng of linearized MRKpAdHVE3 DNA were co-transformed into *E. coli* BJ5183 chemically competent cells. Several clones were selected and grown in 2 ml  
30     Terrific™ broth for 6-8 hours, until turbidity was reached. The total DNA from the cell pellet was purified using Qiagen alkaline lysis and phenol chloroform method. The DNA was precipitated with isopropanol and resuspended in 20 µl dH<sub>2</sub>O. A 2 µl aliquot of this DNA was transformed into *E. coli* XL-1 competent cells. A single colony from each separate transformation was selected and grown overnight in 3 ml  
35     LB +100 µg/ml ampicillin. The DNA was isolated using Qiagen columns. A positive clone was identified by digestion with the restriction enzyme *BstEII* which cleaves

within the gag gene as well as the plasmid backbone. The pre-plasmid clone is designated MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA and is 37,498 bp in size. This strategy was followed to generate E3- and E3+ versions of each of the other gag transgene constructions in both E1 parallel and E1 anti-parallel versions. Figures 7A, 7B and 7C show the various combinations of adenovectors constructed.

## EXAMPLE 10

### Plasmid Competition Studies

A series of plasmid competition studies was carried out. Briefly, the screening of the various combinations of new constructs was performed by mixing equal amounts of each of two competing plasmids. In the experiment shown in Figure 8A, plasmids containing the same transgene but in different orientations were mixed together to create a "competition" between the two plasmids. The aim was to look at the effects of transgene orientation. In the experiment shown in Figure 8B, plasmids containing different polyadenylation signals (but in the same orientation) were mixed together in equal amounts. The aim was to assess effects of polyA signals. Following the initial transfection, the virus was passaged through ten rounds and the viral DNA analyzed by radioactive restriction analysis.

Analysis of the viral species from the plasmid mixing experiment (Figure 8A) showed that adenovectors which had the transgene inserted in the E1 parallel orientation amplified better and were able to out-compete the adenovirus which had the transgene inserted in the E1 anti-parallel orientation. Viral DNA analysis of the mixtures at passage 3 and certainly at passage 6, showed a greater ratio of the virus carrying the transgene in the E1 parallel orientation compared with the E1 antiparallel version. By passage 10, the only viral species observed was the adenovector with the transgene in the E1 parallel orientation for both transgenes tested (hCMV(no intron)-FLgag-bGHpA and hCMV(no intron)-FLgag-SPA).

Analysis of the viral species from the plasmid mixing experiment #2 (Figure 8B) at passages 3 and 6 showed that the polyadenylation signals tested (bGHpA and SPA) did not have an effect on the growth of the virus. Even at passage 10 the two viral species in the mixture were still present in equal amounts.

## EXAMPLE 11

Virus generation of an enhanced adenoviral construct – “MRK Ad5 HIV-1 gag”

The results obtained from the competition study allowed us to make the following conclusions: (1) The packaging signal extension is beneficial; (2) Presence of E3 does enhance viral growth; (3) E1 parallel orientation is recommended; and (4) PolyA signals have no effect on the growth of the adenovirus.

MRK Ad5 HIV-1 gag exhibited the most desirable results. This construct contains the hCMV(no intron)-FLgag-bGHpA transgene inserted into the new E3+ adenovector backbone, MRKpAdHVE3, in the E1 parallel orientation. We have designated this adenovector MRK Ad5 HIV-1 gag. This construct was prepared as outlined below:

The pre-plasmid MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA was digested with *Pac1* to release the vector backbone and 3.3 µg was transfected by calcium phosphate method (Amersham Pharmacia Biotech.) in a 6 cm dish containing PER.C6<sup>®</sup> cells at ~60% confluence. Once CPE was reached (7-10 days), the culture was freeze/thawed three times and the cell debris pelleted. 1 ml of this cell lysate was used to infect into a 6 cm dish containing PER.C6<sup>®</sup> cells at 80-90% confluence. Once CPE was reached, the culture was freeze/thawed three times and the cell debris pelleted. The cell lysate was then used to infect a 15 cm dish containing PER.C6<sup>®</sup> cells at 80-90% confluence. This infection procedure was continued and expanded at passage 6. The virus was then extracted from the cell pellet by CsCl method. Two bandings were performed (3-gradient CsCl followed by a continuous CsCl gradient). Following the second banding, the virus was dialyzed in A105 buffer. Viral DNA was extracted using pronase treatment followed by phenol chloroform. The viral DNA was then digested with *HindIII* and radioactively labeled with [<sup>33</sup>P]dATP. Following gel electrophoresis to separate the digestion products the gel was dried down on Whatman paper and then subjected to autoradiography. The digestion products were compared with the digestion products from the pre-plasmid (that had been digested with *Pac1/HindIII* prior to labeling). The expected sizes were observed, indicating that the virus had been successfully rescued. This strategy was used to rescue virus from each of the various adenovector plasmid constructs prepared.

## EXAMPLE 12

Stability Analyses

To determine whether the various adenovector constructs (e.g., MRK Ad5 HIV-1 gag) show genetic stability, the viruses were each passaged continually. The viral DNA was analyzed at passages 3, 6 and 10. Each virus maintained its correct genetic structure. In addition, the stability of the MRK Ad5 HIV-1 gag was analyzed under propagation conditions similar to that performed in large scale production. For this analysis, the transfections of MRK Ad5 HIV-1 gag as well as three other adenoviral vectors were repeated and the virus was purified at P3. The three other adenovectors were as follows: (1) that comprising hCMV(no intron)-Flgag with a bGHpA terminator in an E3- adenovector backbone; (2) that comprising hCMV(no intron)-Flgag with a SPA termination signal in an E3+ adenovector backbone, and that comprising a mCMV-Flgag with a bGHpA terminator in an E3+ adenovector backbone. All of the vectors have the transgene inserted in the E1 parallel orientation. Viral DNA was analyzed by radioactive restriction analysis to confirm that it was correct before being delivered to fermentation cell culture for continued passaging in serum-free media. At P5 each of the four viruses were purified and the viral DNA extracted for analysis by the restriction digestion and radiolabeling procedure. This virus has subsequently been used in a series of studies (*in vitro* gag expression in COS cells, rodent study and rhesus monkey study) as will be described below. The viruses from P5 are shown in Figure 9.

The passaging under serum-free conditions was continued for the MRKHVE3 (transgene-less, obtained from MRKpAdHVE3 pre-plasmid) and the MRKAd5HIV-1gag (obtained from MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA pre-plasmid) viruses. Figure 10 shows viral DNA analysis by radioactive restriction digestion at passage 11 for MRKHVE3, MRKAd5HIV-1gagE3-, and passage 11 and 12 for MRKAd5HIV-1gag. Aside from the first lane which is the DNA marker lane, the next three lanes are virus from the pre-plasmid controls (controls based on the original virus) - MRKpAdHVE3 (also referred to as "pMRKHVE3"), MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA, and pMRKAd5gag(E3-), respectively. As seen in Figure 10, each of the viral DNA samples show the expected bands with no extraneous bands showing. This signifies that there are no major variant adenovirus species present that can be detected by autoradiography.

Figure 11 shows the results of viral competition study between MRKHVE3 and MRKAd5HIV-1gag. These viruses were mixed together at equal MOI (140 viral

particles each; 280 vp total) at passage 6 and continued to be passaged until P11.

Aside from the first lane which is the DNA marker lane, the next two lanes are the pre-plasmid controls obtained from MRKpAdHVE3 and MRKpAdHVE3+CMV(no intron)-FLgag-bGHpA. The next two lanes are the viral DNA from the starting viral

5 material at passage six. The last two lanes are the competition studies performed in duplicate. The data in Figure 11 shows the effect the gag transgene in culture.

Growth of a MRKAd5gag virus was compared with growth of a "transgene-less" MRKHVE3. These two viruses were infected at the same MOI (i.e. 140 vp each) at passage 6 and then passaged through to passage 11 and the viral pool was analyzed by  
10 radioactive restriction analysis. The data shows that one virus did not out compete the other. Therefore, the gag transgene did not show obvious signs of toxicity to the adenovirus.

Analysis by *HindIII* digestion shows that each virus specie is present in approximately equal amounts. As above, there does not appear to be signs of any  
15 extraneous bands. Figure 12 shows higher passage numbers for MRKAd5HIV-1gag grown under serum-containing conditions. The genome integrity again has been maintained and there is no evidence of rearrangements, even at the highest passage level (P21).

Each of the four vectors shown in Figure 9 were analyzed for amplification  
20 capacity. Table 4 below shows the QPA analysis used in the estimation of viral amplification ratios at P4. The determination of the amplification ratio for the original HIV-1 gag construct is based on the clinical lot at P12. It has been shown that amplification rates increases with higher passage number for the original virus. The reason for this observation is due to the emergence of variants which exhibit  
25 increased growth rates compared to the intact adenovector. With continued passaging of the original Ad gag vector, the level of variants increases and hence amplification rates increase also.

The MRK Ad5 HIV-1 gag virus has also been continually passaged under process conditions (i.e., serum-free media). Viral DNA extracted from passages 11  
30 and 12 show no evidence of rearrangement.

Table 4:  
Amplification Ratios Based on AEX and QPA Analysis of  
Virus Amplification from Passage 3 to Passage 4.

Ad gag construct	Amplification Ratio
MRKAd5gag	470
HCMV-Flgag-bGHpA [E3-]	115
HCMV-Flgag-SPA [E3+]	320
mCMV-FLgag-bGHpA [E3+]	420
Original construct *	40 - 50

\* This estimation is based on the clinical lot growth characteristics at Passage 12.

### EXAMPLE 13

#### Analytical Evaluation of the enhanced Ad5 Constructs

To study the effects of the transgene and the E3 gene on virus amplification, the enhanced adenoviral vector, MRK Ad5 HIV-1 gag, along with its transgene-less version (MRKpAdHVE3) and its E3- version (MRK Ad5 HIV-1 gag E3-), was studied for several passages under serum-free conditions. Table 5A shows the amplification ratios determined for passages P3 to P8 for MRK Ad5 HIV-1 gag. Within a certain MOI range, it has been determined that the virus output is directly proportional to the virus input. Therefore, the greater the number of virus particles per cell at infection, the greater the virus amount produced. Viral amplification ratios, on the other hand, are inversely proportional to the virus input. The lower the virus input, the greater the amplification ratio.

Table 5B shows the amplification rates of the new E3+ vector backbone MRKpAdHVE3. It has a significantly lower rate of amplification compared with the gag transgene containing version. This may be contributed to the larger size MRK Ad5 HIV-1 gag since it contains the transgene. This inclusion of the transgene brings the size of the adenovirus closer to the size of a wild type Ad5 virus. It is well known that adenoviruses amplify best when they are at close to their wild type genomic size.

Wild type Ad5 is 35,935 bp. The MRKpAdHVE3 is 32,905 bp in length. The enhanced adenovector MRK Ad5 HIV-1 gag is 35,453bp (See Figure 14 for vector map; see also Figure 15A-X show the complete pre-adenoviral vector sequence, which includes an additional 2,021 bp of the vector backbone).

- 5        Table 5C shows the amplification rates of the new E3- gag containing virus MRK Ad5 HIV-1 gag E3-. Once again, this virus shows lower growth rate than the enhanced adenoviral vector. This may be attributed to the decreased sized of this virus (due to the E3 gene deletion) compared with wild type Ad5. The MRK Ad5 HIV-1 gag E3- virus is 32,810 bp in length. This can be compared with the wild type
- 10    Ad5 which is 35,935 bp and MRK Ad5 HIV-1 gag which is 35,453 bp in length.

**Table 5A:** Amplification ratios determined by AEX and QPA for MRKAd5gag over several continuous passaging in serum free media. Following P5, two replicate samples were taken (rep-1 and rep-2) and analyzed.

### MRKAd5gag rep1

	Xv (10 <sup>6</sup> cells/ml), Infection	Viability (%) Harvest	Harvest Time h.p.L	Cell Passage Number	Titer 10 <sup>6</sup> vp/ml culture	Titer 10 <sup>6</sup> vp/cell	QPA 10 <sup>6</sup> TCID <sub>50</sub> /ml	Ratio AEX:QPA	Amplification Ratio	AEX Internal Control
P4	1.49, 81%	0.59, 50%	44	46	8.7	5.9	1.72	50	470 (MOI = 125)	
P5	1.38, 93%	0.66, 47%	48	49	6.7	4.9	1.38	49	170	
P6	1.04, 94%	0.68, 77%	47	48	5.8	5.6	1.42	41	200	
P7	1.50, 84%	0.96, 61%	48.5	50	3.9	1.4	0.97	40	50	
P7	1.09, 97%	0.76, 69%	50	52	5.2	4.7	1.70	31	170	
P8	1.03, 94%	0.86, 64%	47.5	54	9.0	6.7	1.10	82	310	
P9	0.89, 95%	0.99, 73%	47.5	56	4.4	4.9	1.03	43	175	3.12 2.84
P10	1.09, 91%	1.06, 66%	47.5	58	3.0	2.6	1.16	26	100	2.70 2.60
P11	1.19, 88%	0.98, 65%	47	60	3.6	3.0	1.15	31	110	2.70 2.70
P12	0.98, 91%	0.85, 63%	47.5	47	5.4	5.5	1.20	45	200	2.86 2.60
P13	1.00, 88%	0.70, 67%	49	49	5.8	5.8	1.11	62	210	3.18 3.18
P14	1.94, 92%	0.88, 67%	46	63	6.6	4.4			160	3.28 3.27
P15	0.97, 96%	0.84, 66%	47	47	6.9	7.1			250	3.12 2.91

**Table 5B:** Amplification ratios determined by AEX and QPA for MRKHVE3 over several continuous passaging in serum free media. MRKHVE3 is the new vector backbone which does NOT carry a transgene.

### MRKHVE3

	Xv (10 <sup>6</sup> cells/ml), Infection	Viability (%) Harvest	Harvest Time h.p.L	Cell Passage Number	Titer 10 <sup>6</sup> vp/ml culture	Titer 10 <sup>6</sup> vp/cell	QPA 10 <sup>6</sup> TCID <sub>50</sub> /ml	Ratio AEX:QPA	Amplification Ratio	AEX Internal Control
P4	1.10, 97%	1.28, 78%	49	54	4.1	3.8	1.70	25	300 (MOI = 125)	
P5	0.92, 89%	1.18, 77%	47	48	4.3	4.7	1.24	35	170	
P6	1.55, 86%	1.26, 76%	49.5	50	1.2	0.8	0.56	21	30	
P6	1.09, 97%	1.11, 81%	49	52	4.0	3.6	1.16	34	130	
P7	1.17, 91%	1.22, 91%	47.5	54	3.7	3.2	0.50	74	110	
P8	0.98, 88%	1.41, 83%	48	56	2.1	2.1	0.47	45	75	3.12 2.84
P9	1.20, 89%	1.28, 81%	47.5	58	0.8	0.7	0.29	28	25	2.70 2.60
P10	0.99, 82%	1.55, 86%	47	60	2.3	2.3	0.43	53	80	2.70 2.70
P11	1.07, 98%	1.25, 83%	48	47	2.7	2.5	0.41	66	90	2.86 2.60
P12	0.80, 91%	1.14, 80%	49.5	49	5.9	7.4	0.48	123	260	3.18 3.18
P13	1.86, 95%	1.14, 85%	45.5	53	5.8	3.0			110	3.28 3.27
P14	0.97, 96%	1.03, 98%	48.5	47	9.4	9.7			350	3.12 2.91
P15	0.87, 99%	0.87, 69%	49.5	49	5.3	6.1			218	2.78 2.52

Table 5C. Amplification ratios determined by AEX and QPA for MRKAd5gag(E3-) over several continuous passaging in serum free media. This construct is identical to the MRKAd5gag construct except that this version is DELETED of the E3 gene.

5

### MRKAd5gag(E3-)

	Xv (10 <sup>6</sup> cells/ml), Infection	Viability (%), Harvest	Harvest Time h.p.i.	Cell Passage Number	Titer 10 <sup>7</sup> vp/ml culture	Titer 10 <sup>4</sup> vp/cell	QPA 10 <sup>6</sup> TCID <sub>50</sub> /ml	Ratio AEX:QPA	Amplification Ratio	AEX Internal Control
P4	1.62, 77%	1.12, 62%	47.5	46	2.0	1.2	0.92	20	100 (MDI=125)	
P5	1.16, 92%	0.62, 43%	49	49	3.3	2.9	0.99	34	100	
P6	1.71, 86%	0.20, 10%	49	50	4.7	2.7	1.70	28	100	
P6	1.09, 87%	0.63, 54%	49.5	52	5.4	5.0	1.76	31	180	
P7	1.17, 91%	0.98, 72%	47.50	54	7.1	6.1	0.67	106	220	
P8	0.98, 88%	0.77, 48%	48	56	3.1	3.2	0.66	47	115	3.12 2.84
P9	1.20, 89%	1.03, 72%	48	58	1.8	1.5	0.57	32	55	2.70 2.60
P10	0.99, 82%	0.80, 62%	46.5	60	3.2	3.2	0.58	47	115	2.70 2.70
P11	1.07, 96%	0.98, 70%	48.5	47	5.9	5.5	0.68	87	200	2.86 2.60
P12	0.80, 91%	0.67, 59%	50	49	5.1	6.4	0.72	71	230	3.18 3.18
P13	1.98, 95%	0.91, 59%	45.5	53	7.4	3.8			135	3.28 3.27
P14	0.97, 96%	0.81, 74%	48	47	6.8	7.0			250	3.12 2.91
P15	0.87, 99%	0.84, 56%	49	49	4.8	5.5			196	2.78 2.52

### EXAMPLE 14

#### Gag Expression Analysis of the Novel Constructs

*In vitro* gag analysis of the MRK Ad5 HIV-1 gag and the original HIV-gag vectors (research and clinical lot) show comparable gag expression. The clinical lot shows only a slightly reduced gag expression level. The most noticeable difference is with the mCMV vector. This vector shows roughly 3 fold lower expression levels compared with the other vectors tested (which all contain hCMV promoters). The mCMV-FLgag with bGHpA assay was performed three times using different propagation and purification lots and it consistently exhibited weaker gag expression.

### EXAMPLE 15

#### Evaluation of MRK Ad5 HIV-1 gag and Other gag-Containing Adenovectors in Balb/c Mice

Cohorts of 10 balb/c mice were vaccinated intramuscularly with escalating doses of MRK Ad5 HIV-1 gag, and the research and clinical lots of original Ad5HIV-1gag. Serum samples were collected 3 weeks post dose 1 and analyzed by anti-p24 sandwich ELISA.

Anti-p24 titers in mice that received MRK Ad5 HIV-1 gag ( $10^7$  and  $10^9$  vp(viral particle) doses) were comparable (Figure 13) to those of the research lot of Ad5HIV-1 gag, for which much of the early rhesus data were generated on. These titers were also comparable when E3 is deleted (MRKAd5hCMVgagbGHpA(E3-)) or SPA is substituted for bGHpA terminator (MRKAd5 hCMV-gag-SPA (E3+)) or murine CMV promoter is used in place of hCMV (MRKAd5 mCMV-gag-bGHpA (E3+)) in the MRKAd5 backbone.

The results shown in Table 7 indicate that the three other vectors ( in addition to the preferred vector, MRK Ad5 HIV-1 gag, are also capable of inducing strong anti-gag antibody responses in mice. Interestingly enough, while the mCMV-FLgag construct containing bGHpA and E3+ in an E1 parallel orientation showed lowest gag expression in the COS cell *in vitro* infection (Table 6) in comparison with the other vectors tested, it generated the greatest anti-gag antibody response this *in vivo* Balb/c study. Table 7 also shows a dose response in anti-gag antibody production in both the research and the clinical lot. As expected, the clinical lot shows reduced anti-gag antibody induction at each dosage level compared to the same dosage used for the research lot.

Table 6: *In vitro* analysis for gag expression in COS cells by Elisa assay.

Viral Vectors <sup>a</sup>	$\mu\text{g gag}/4.8 \times 10^5 \text{ COS}/10^8 \text{ parts}/48\text{hr}$
MRKAd5gag <sup>b</sup>	1.40
Clinical lot Ad5gag <sup>c</sup>	1.28
Research lot Ad5gag <sup>d</sup>	1.32
MCMVFL-gagbGHpA <sup>e</sup>	0.42

<sup>a</sup>  $A_{260\text{nm}}$  absorbance readings taken for viral particle determinations.

<sup>b</sup> MRKAd5gag was produced in serum free conditions and purified at P5.

<sup>c</sup> Clinical lot# Ad5gagFN0001

<sup>d</sup> Research Ad5FLgag lot# 6399

<sup>e</sup> mCMVFL-gagbGHpA was produced in serum free conditions and purified at P5.

**Table 7:** mHIV020 Anti-p24 Ab Titers in Balb/c mice (n=10) vaccinated with various Adgag constructs and lots (3 week post dose1).

Group ID	Vaccine	Dose (vp)	GMT	SE upper	SE lower
1	<sup>a</sup> MRKAd5gag	10 <sup>7</sup>	25600	5877	4780
2	"	10 <sup>9</sup>	409600	94028	76473
3	hCMV FL-gag bGHpA [E3-] →	10 <sup>7</sup>	7352	2077	1620
4	"	10 <sup>9</sup>	235253	59767	47659
5	hCMV FL-gag SPA [E3+] →	10 <sup>7</sup>	12800	9905	236
6	"	10 <sup>9</sup>	310419	99181	75165
7	<sup>b</sup> mCMV FL-gag bGHpA [E3+] →	10 <sup>7</sup>	44572	23504	15389
8	"	10 <sup>9</sup>	941014	239068	190636
9	<sup>c</sup> hCMV FL-gag bGHpA [E3-] ←	10 <sup>7</sup>	3676	934	745
10	"	10 <sup>9</sup>	117627	17491	15227
11	research lot hCMV intronA FL-gag bGHpA [E3-] <-	10 <sup>6</sup>	528	262	175
12	"	10 <sup>7</sup>	14703	5274	3882
13	"	10 <sup>8</sup>	58813	14942	11915
14	"	10 <sup>9</sup>	204800	53232	42250
15	clinical lot hCMVintronA FL-gag bGHpA [E3-] <-	10 <sup>6</sup>	230	82	61
16	"	10 <sup>7</sup>	4222	3405	1138
17	"	10 <sup>8</sup>	19401	3939	3274
18	"	10 <sup>9</sup>	89144	25187	19639
19	Naïve	none	93	7	6

\*2x50 µL i.m. (quad) injections/animal

P.I.s: Youli, Chen, Casimiro

Vaccination: T. Toner, Q. Su

Assay: M. Chen

<sup>a</sup>The structure of MRKAd5gag is: hCMVFL-gagbGHpA [E3+] → The same lot of MRKAd5gag used in this rodent study was used in the Rhesus monkey study (Tables 7 and 8).

<sup>b</sup>The same lot of mCMVFL-gagbGHpA[E3+] used in the *in vitro* study (Table 6) was used here.

<sup>c</sup>This construct was designed by Volker Sandig. It contains a shorter version of the hCMV promoter than that used in the MRK constructs. The adenovector backbone is identical to the original backbone used in the original Adgag vector. Expression at 10<sup>6</sup> dose from this vector is 7 fold lower than the same dose of the MRKAd5gag and 4 fold lower than the research lot.

### EXAMPLE 16

#### Comparison of Humoral and Cellular Responses Towards the Original Ad-gag Construct with the New MRK Ad5 HIV-1 gag in Rhesus Monkeys

- 5 Cohorts of 3 rhesus monkeys were vaccinated intramuscularly with MRK Ad5 HIV-1 gag or the clinical Ad5gag bulk at two doses, 10<sup>11</sup> vp and 10<sup>9</sup> vp. Immunizations were conducted at week 0, 4, and 25. Serum and PBMC samples were collected at selected time points. The serum sample were assayed for anti-p24 Ab titers (using competitive based assay) and the PBMCs for antigen-specific IFN-  
10 gamma secretion following overnight stimulation with gag 20-mer peptide pool (via ELISpot assay).

The results shown in Table 8 indicate comparable responses with respect to the generation of anti-gag antibodies. The frequencies of gag-specific T cells in

- peripheral blood assmumarized in Table 9 demonstrate a strong cellular immune response generated after a single dose with the new construct MRK Ad5 HIV-1 gag. The responses are also boostable with second dose of the same vector. The vector is also able to induce CD8+ T cell responses (as evident by remaining spot counts after
- 5 CD4+ depletion of PBMCs) which are responsible for cytotoxic activity.

Table 8 Anti-p24 antibody titers (in mMU/mL) in rhesus macaques immunized with gag-expressing adenovectors (Protocol HIV203).

Vaccine	Pre	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 25	Wk 28
MRKAd5gag <sup>a</sup> , 10 <sup>11</sup> vp								
97N010	<10	118	5528	11523	7062	21997	ND	51593
97N116	<10	62	772	1447	1562	2174	ND	20029
98X007	<10	66	3353	6156	6845	3719	ND	24031
MRKAd5gag, 10 <sup>9</sup> vp								
97N120	<10	51	204	318	366	482	ND	6550
97N144	<10	18	118	274	706	888	ND	7136
98X008	<10	15	444	386	996	1072	ND	12851
Ad5gag <sup>b</sup> , Clinical Lot, 10 <sup>11</sup> vp								
97X001	<10	87	2579	4718	7174	7250	ND	69226
97N146	<10	72	3604	7380	7526	18906	ND	60283
98X009	<10	78	4183	3946	3124	6956	ND	26226
Ad5gag, Clinical Lot, 10 <sup>9</sup> vp								
97N020	<10	<10	143	371	390	1821	ND	17177
97X003	<10	<10	39	93	156	596	ND	2053
98X012	<10	81	342	717	956	1558	ND	11861
<sup>a</sup> MRKAd5gag (hCMV, bGHPA, E3+)								
<sup>b</sup> Original Ad5gag vector (hCMV/Intron A, bGHPA, E3-), lot#FN0001								
ND, not determined								

Table 9. Number of gag-specific T cells per million peripheral blood mononuclear cells (PBMCs) in rhesus monkeys immunized with gag-expressing adenovectors. Also included are those frequencies in PBMCs depleted of CD4<sup>+</sup> T cells.

Grp #	Vaccination T=0,4,25 wks	Monkey ID	T=4 Wk		T=6 Wk		T=11 Wk		T=16 Wk		T=25 Wk		T=28 Wk	
			Media <sup>a</sup>	Gag H <sup>b</sup>	Media	Gag H	Media	Gag H	Media	Gag H	Media	Gag H	Media	Gag H
1	MRKAd5gag 10 <sup>9</sup> vp	97ND10	6	89	0	395	0	1058	0	1174	3	775	4	1074
		97ND10(CD4-)	4	38			3	993			0	76	0	594
		97N116	1	386	1	609	0	534	4	395	1	261	0	408
		97N116(CD4-)	11	676			0	593			0	184	0	666
		98X007	10	579	0	1304	3	2193	1	2118	3	1588	0	2113
		98X007(CD4-)	20	965			0	2675			0	1656	0	1278
2	MRKAd5gag 10 <sup>9</sup> vp	97N120	5	275	1	249	4	141	4	119	9	206	4	219
		97N120(CD4-)	11	170			0	85			0	75	1	219
		97N144	3	236	6	438	1	318	3	256	1	98	5	373
		97N144(CD4-)	6	148			0	285			ND	ND	0	625
		98X008	4	368	1	1090	3	891	4	673	3	473	5	735
		98X008(CD4-)	14	696			0	1175			0	391	4	848
3	Ad5gag clinical lot 10 <sup>9</sup> vp	97X001	0	261	1	485	0	817	0	1220b	1	894	0	1858
		97X001(CD4-)	10	283			3	996			0	1010	0	1123
		97N146	3	150	1	465	0	339	1	1272	3	1238	3	1785
		97N146(CD4-)	6	133			0	370			0	654	0	971
		98X009	0	83	3	339	3	559	0	896	1	384	0	1748
		98X009(CD4-)	0	73			0	333			0	225	0	644
4	Ad5gag clinical lot 10 <sup>9</sup> vp	97ND20	3	30	1	101	0	66	0	36	0	26	0	41
		97ND20(CD4-)	10	29			0	15			0	1	0	16
		97X003	4	68	5	134	0	18	1	38	4	38	6	81
		97X003(CD4-)	9	40			0	6			0	4	0	19
		98X012	5	95	3	54	1	34	0	18	0	20	1	121
		98X012(CD4-)	11	70			0	11			0	8	0	41
5	Naïve	96RD41	6	8	1	16	0	0	0	0	0	0	1	0
		053F	14	18	5	16	20	14	19	15	10	15	24	9

Based on either 4x10<sup>5</sup> or 2x10<sup>5</sup> cells per well (depending on spot density)

ND, not determined

<sup>a</sup>Track or no peptide control

<sup>b</sup>Pool of 20-aa peptides overlapping by 10 aa and encompassing the gag sequence

The adenovectors described herein and, particularly, MRK Ad5 HIV-1 gag, represent very promising HIV-gag adenovectors with respect to their enhanced growth characteristics in both serum and, more importantly, in serum-free media conditions. In comparison with the current HIV-1 gag adenovector construct, MRK Ad5 HIV-1 gag shows a 5-10 fold increased amplification rate. We have shown that it is genetically stable at passage 21. This construct is able to generate significant cellular immune responses *in vivo* even at a relatively low dose of 10<sup>9</sup> vp. The potency of the MRKAd5gag construct is comparable to, if not better than the original HIV-1 gag vector as shown in this rhesus monkey study.

#### EXAMPLE 17

#### CODON OPTIMIZED HIV-1 POL AND CODON OPTIMIZED HIV-1 POL MODIFICATIONS

The open reading frames for the various synthetic *pol* genes disclosed herein comprise coding sequences for the reverse transcriptase (or RT which consists of a polymerase and RNase H activity) and integrase (IN). The protein sequence is based

on that of Hxb2r, a clonal isolate of IIIB; this sequence has been shown to be closest to the consensus clade B sequence with only 16 nonidentical residues out of 848 (Korber, et al., 1998, Human retroviruses and AIDS, Los Alamos National Laboratory, Los Alamos, New Mexico). The skilled artisan will understand after review of this specification that any available HIV-1 or HIV-2 strain provides a potential template for the generation of HIV pol DNA vaccine constructs disclosed herein. It is further noted that the protease gene is excluded from the DNA vaccine constructs of the present invention to insure safety from any residual protease activity in spite of mutational inactivation. The design of the gene sequences for both wild-type (wt-pol) and inactivated pol (IA-pol) incorporates the use of human preferred ("humanized") codons for each amino acid residue in the sequence in order to maximize *in vivo* mammalian expression (Lathe, 1985, *J. Mol. Biol.* 183:1-12). As can be discerned by inspecting the codon usage in SEQ ID NOs: 1, 3, 5 and 7, the following codon usage for mammalian optimization is preferred: Met (ATG), Gly (GGC), Lys (AAG), Trp (TGG), Ser (TCC), Arg (AGG), Val (GTG), Pro (CCC), Thr (ACC), Glu (GAG); Leu (CTG), His (CAC), Ile (ATC), Asn (AAC), Cys (TGC), Ala (GCC), Gln (CAG), Phe (TTC) and Tyr (TAC). For an additional discussion relating to mammalian (human) codon optimization, see WO 97/31115 (PCT/US97/02294), which, as noted elsewhere in this specification, is hereby incorporated by reference. It is intended that the skilled artisan may use alternative versions of codon optimization or may omit this step when generating HIV pol vaccine constructs within the scope of the present invention. Therefore, the present invention also relates to non-codon optimized versions of DNA molecules and associated recombinant adenoviral HIV vaccines which encode the various wild type and modified forms of the HIV Pol protein disclosed herein. However, codon optimization of these constructs is a preferred embodiment of this invention.

A particular embodiment of this portion of the invention comprises codon optimized nucleotide sequences which encode wt-pol DNA constructs (herein, "wt-pol" or "wt-pol (codon optimized)") wherein DNA sequences encoding the protease (PR) activity are deleted, leaving codon optimized "wild type" sequences which encode RT (reverse transcriptase and RNase H activity) and IN integrase activity. A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:1, the open reading frame being contained from an initiating Met residue at nucleotides 10-12 to a termination codon from nucleotides 2560-2562. SEQ ID NO:1 is as follows:

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AGATCTACCA TGGCCCCCAT CTCCCCCAT GAGACTGTGC CTGTGAAGCT GAAGCCTGGC
ATGGATGGCC CCAAGGTGAA GCAGTGGCCC CTGACTGAGG AGAAGATCAA GGCCCTGGTG

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GAAATCTGCA CTGAGATGGA GAAGGAGGGC AAAATCTCCA AGATTGGCCC CGAGAACCCC  
TACAACACCC CTGTGTTTGC CATCAAGAAG AAGGACTCCA CCAAGTGGAG GAAGCTGGTG  
GACTTCAGGG AGCTGAACAA GAGGACCCAG GACTTCTGGG AGGTGCAGCT GGGCATCCCC  
CACCCCCTG GCCTGAAGAA GAAGAAGTCT GTGACTGTGC TGGATGTGGG GGATGCCTAC  
5 TTCTCTGTGC CCCTGGATGA GGACTTCAGG AAGTACACTG CCTTCACCAT CCCCTCCATC  
AACAATGAGA CCCCTGGCAT CAGGTACCAG TACAATGTGC TGCCCCAGGG CTGGAAGGGC  
TCCCCTGCCA TCTTCCAGTC CTCCATGACC AAGATCCTGG AGCCCTTCAG GAAGCAGAAC  
CCTGACATTG TGATCTACCA GTACATGGAT GACCTGTATG TGGGCTCTGA CCTGGAGATT  
GGGCAGCACA GGACCAAGAT TGAGGAGCTG AGGCAGCACC TGCTGAGGTG GGGCCTGACC  
10 ACCCCTGACA AGAAGCACCA GAAGGAGCCC CCCTTCCTGT GGATGGGCTA TGAGCTGCAC  
CCCGACAAGT GGACTGTGCA GCCCATTTGTG CTGCCCTGAGA AGGACTCCTG GACTGTGAAT  
GACATCCAGA AGCTGGTGGG CAAGCTGAAC TGGGCTCCC AAATCTACCC TGGCATCAAG  
GTGAGGCAGC TGTGCAAGCT GCTGAGGGGC ACCAAGGCCC TGACTGAGGT GATCCCCCTG  
ACTGAGGAGG CTGAGCTGGA GCTGGCTGAG AACAGGGAGA TCCTGAAGGA GCCTGTGCAT  
15 GGGGTGTACT ATGACCCCTC CAAGGACCTG ATTGCTGAGA TCCAGAAGCA GGGCCAGGGC  
CAGTGGACCT ACCAAATCTA CCAGGAGCCC TTCAAGAACC TGAAGACTGG CAAGTATGCC  
AGGATGAGGG GGGCCACAC CAATGATGTG AAGCAGCTGA CTGAGGCTGT GCAGAAGATC  
ACCACTGAGT CCATTGTGAT CTGGGGCAAG ACCCCCAAGT TCAAGCTGCC CATCCAGAAG  
GAGACCTGGG AGACCTGGTG GACTGAGTAC TGGCAGGCCA CCTGGATCCC TGAGTGGGAG  
20 TTTGTGAACA CCCCCCCTT GGTGAAGCTG TGGTACCAGC TGGAGAAGGA GCCCATTTGTG  
GGGGCTGAGA CCTTCTATGT GGATGGGGCT GCCAACAGGG AGACCAAGCT GGGCAAGGCT  
GGCTATGTGA CCAACAGGGG CAGGCAGAAG GTGGTGACCC TGACTGACAC CACCAACCAG  
AAGACTGAGC TCCAGGCCAT CTACCTGGCC CTCCAGGACT CTGGCCTGGA GGTGAACATT  
GTGACTGACT CCCAGTATGC CCTGGGCATC ATCCAGGCC AGCCTGATCA GTCTGAGTCT  
25 GAGCTGGTGA ACCAGATCAT TGAGCAGCTG ATCAAGAAGG AGAAGGTGTA CCTGGCCTGG  
GTGCCTGCCC ACAAGGGCAT TGGGGGCAAT GAGCAGGTGG ACAAGCTGGT GTCTGCTGGC  
ATCAGGAAGG TGCTGTTCCCT GGATGGCATT GACAAGGCCC AGGATGAGCA TGAGAAGTAC  
CACTCCAAT GGAGGGCTAT GGCTCTGAC TTCAACCTGC CCCCTGTGGT GGCTAAGGAG  
ATTGTGGCCT CCTGTGACAA GTGCCAGCTG AAGGGGGAGG CCATGCATGG GCAGGTGGAC  
30 TGCTCCCCTG GCATCTGGCA GCTGGACTGC ACCCACCTGG AGGGCAAGGT GATCCTGGTG  
GCTGTGCATG TGGCCTCCGG CTACATTGAG GCTGAGGTGA TCCCTGCTGA GACAGGCCAG  
GAGACTGCCT ACTTCCTGCT GAAGCTGGCT GGCAGGTGGC CTGTGAAGAC CATCCACACT  
GACAATGGCT CCAACTTCAC TGGGGCCACA GTGAGGGCTG CCTGCTGGTG GGCTGGCATC  
AAGCAGGAGT TTGGCATCCC CTACAACCCC CAGTCCCAGG GGGTGGTGA GTCCATGAAC  
35 AAGGAGCTGA AGAAGATCAT TGGGCAGGTG AGGGACCAGG CTGAGCACCT GAAGACAGCT  
GTGCAGATGG CTGTGTTTCAT CCACAACCTC AAGAGGAAGG GGGGCATCGG GGGCTACTCC

GCTGGGGAGA GGATTGTGGA CATCATTGCC ACAGACATCC AGACCAAGGA GCTCCAGAAG  
 CAGATCACCA AGATCCAGAA CTTGAGGGTG TACTACAGGG ACTCCAGGAA CCCCCTGTGG  
 AAGGGCCCTG CCAAGCTGCT GTGGAAGGGG GAGGGGGCTG TGGTGATCCA GGACAACTCT  
 GACATCAAGG TGGTGCCAG GAGGAAGGCC AAGATCATCA GGGACTATGG CAAGCAGATG  
 5 GCTGGGGATG ACTGTGTGGC CTCCAGGCAG GATGAGGACT AAAGCCCGGG CAGATCT (SEQ  
 ID NO:1).

The open reading frame of the wild type pol construct disclosed as SEQ ID  
 NO:1 contains 850 amino acids, disclosed herein as SEQ ID NO:2, as follows:

Met Ala Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro  
 10 Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys  
 Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys  
 Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala  
 Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg  
 Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile  
 15 Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Asp  
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys  
 Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile  
 Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala  
 Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln  
 20 Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Asp Asp Leu Tyr Val Gly  
 Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu Arg  
 Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His Gln  
 Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys  
 Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val  
 25 Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile  
 Tyr Pro Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr  
 Lys Ala Leu Thr Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu  
 Leu Ala Glu Asn Arg Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr  
 Tyr Asp Pro Ser Lys Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln  
 30 Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys  
 Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr Asn Asp Val Lys  
 Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile  
 Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp  
 Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp  
 35 Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu  
 Lys Glu Pro Ile Val Gly Ala Glu Thr Phe Tyr Val Asp Gly Ala Ala

Asn Arg Glu Thr Lys Leu Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly  
 Arg Gln Lys Val Val Thr Leu Thr Asp Thr Thr Asn Gln Lys Thr Glu  
 Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp Ser Gly Leu Glu Val Asn  
 Ile Val Thr Asp Ser Gln Tyr Ala Leu Gly Ile Ile Gln Ala Gln Pro  
 5 Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln Leu Ile  
 Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile  
 Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys  
 Val Leu Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys  
 Tyr His Ser Asn Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro  
 10 Val Val Ala Lys Glu Ile Val Ala Ser Cys Asp Lys Cys Gln Leu Lys  
 Gly Glu Ala Met His Gly Gln Val Asp Cys Ser Pro Gly Ile Trp Gln  
 Leu Asp Cys Thr His Leu Glu Gly Lys Val Ile Leu Val Ala Val His  
 Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly  
 Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val  
 15 Lys Thr Ile His Thr Asp Asn Gly Ser Asn Phe Thr Gly Ala Thr Val  
 Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro  
 Tyr Asn Pro Gln Ser Gln Gly Val Val Glu Ser Met Asn Lys Glu Leu  
 Lys Lys Ile Ile Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr  
 Ala Val Gln Met Ala Val Phe Ile His Asn Phe Lys Arg Lys Gly Gly  
 20 Ile Gly Gly Tyr Ser Ala Gly Glu Arg Ile Val Asp Ile Ile Ala Thr  
 Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln Ile Thr Lys Ile Gln Asn  
 Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu Trp Lys Gly Pro  
 Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln Asp Asn  
 Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp  
 25 Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp  
 Glu Asp (SEQ ID NO:2).

The present invention especially relates to an adenoviral vector vaccine which  
 comprises a codon optimized HIV-1 DNA pol construct wherein, in addition to  
 deletion of the portion of the wild type sequence encoding the protease activity, a  
 30 combination of active site residue mutations are introduced which are deleterious to  
 HIV-1 pol (RT-RH-IN) activity of the expressed protein. Therefore, the present  
 invention preferably relates to an adenoviral HIV-1 DNA pol-based vaccine wherein  
 the construct is devoid of DNA sequences encoding any PR activity, as well as  
 containing a mutation(s) which at least partially, and preferably substantially,  
 35 abolishes RT, RNase and/or IN activity. One type of HIV-1 pol mutant which is part  
 and parcel of an adenoviral vector vaccine may include but is not limited to a mutated

DNA molecule comprising at least one nucleotide substitution which results in a point mutation which effectively alters an active site within the RT, RNase and/or IN regions of the expressed protein, resulting in at least substantially decreased enzymatic activity for the RT, RNase H and/or IN functions of HIV-1 Pol. In a preferred embodiment of this portion of the invention, a HIV-1 DNA pol construct contains a mutation or mutations within the Pol coding region which effectively abolishes RT, RNase H and IN activity. An especially preferable HIV-1 DNA pol construct in a DNA molecule which contains at least one point mutation which alters the active site of the RT, RNase H and IN domains of Pol, such that each activity is at least substantially abolished. Such a HIV-1 Pol mutant will most likely comprise at least one point mutation in or around each catalytic domain responsible for RT, RNase H and IN activity, respectfully. To this end, an especially preferred HIV-1 DNA pol construct is exemplified herein and contains nine codon substitution mutations which results in an inactivated Pol protein (IA Pol: SEQ ID NO:4, Figure 17A-C) which has no PR, RT, RNase or IN activity, wherein three such point mutations reside within each of the RT, RNase and IN catalytic domains. Therefore, an especially preferred exemplification is an adenoviral vaccine which comprises, in an appropriate fashion, a DNA molecule which encodes IA-pol, which contains all nine mutations as shown below in Table 1. An additional preferred amino acid residue for substitution is Asp551, localized within the RNase domain of Pol. Any combination of the mutations disclosed herein may suitable and therefore may be utilized as an IA-Pol-based vaccine of the present invention. While addition and deletion mutations are contemplated and within the scope of the invention, the preferred mutation is a point mutation resulting in a substitution of the wild type amino acid with an alternative amino acid residue.

Table 1

	<u>wt aa</u>	<u>aa residue</u>	<u>mutant aa</u>	<u>enzyme function</u>
	Asp	112	Ala	RT
	Asp	187	Ala	RT
30	Asp	188	Ala	RT
	Asp	445	Ala	RNase H
	Glu	480	Ala	RNase H
	Asp	500	Ala	RNase H
	Asp	626	Ala	IN
35	Asp	678	Ala	IN
	Glu	714	Ala	IN

It is preferred that point mutations be incorporated into the IAPol mutant adenoviral vaccines of the present invention so as to lessen the possibility of altering epitopes in and around the active site(s) of HIV-1 Pol.

To this end, SEQ ID NO:3 discloses the nucleotide sequence which codes for a codon optimized pol in addition to the nine mutations shown in Table 1, disclosed as follows, and referred to herein as "IAPol":

5 AGATCTACCA TGGCCCCCAT CTCCCCATT GAGACTGTGC CTGTGAAGCT GAAGCCTGGC  
ATGGATGGCC CCAAGGTGAA GCAGTGGCCC CTGACTGAGG AGAAGATCAA GGCCCTGGTG  
GAAATCTGCA CTGAGATGGA GAAGGAGGGC AAAATCTCCA AGATTGGCCC CGAGAACCCC  
10 TACAACACCC CTGTGTTTGC CATCAAGAAG AAGGACTCCA CCAAGTGGAG GAAGCTGGTG  
GACTTCAGGG AGCTGAACAA GAGGACCCAG GACTTCTGGG AGGTGCAGCT GGGCATCCCC  
CACCCCGCTG GCCTGAAGAA GAAGAAGTCT GTGACTGTGC TGGCTGTGGG GGATGCCTAC  
TTCTCTGTGC CCCTGGATGA GGACTTCAGG AAGTACACTG CCTTCACCAT CCCCTCCATC  
AACAATGAGA CCCCTGGCAT CAGGTACCAG TACAATGTGC TGCCCCAGGG CTGGAAGGGC  
15 TCCCCTGCCA TC'TTCCAGTC CTCCATGACC AAGATCCTGG AGCCCTTCAG GAAGCAGAAC  
CCTGACATTG TGATCTACCA GTACATGGCT GCCCTGTATG TGGGCTCTGA CCTGGAGATT  
GGGCAGCACA GGACCAAGAT TGAGGAGCTG AGGCAGCACC TGCTGAGGTG GGGCCTGACC  
ACCCCTGACA AGAAGCACCA GAAGGAGCCC CCCTTCCTGT GGATGGGCTA TGAGCTGCAC  
CCCGACAAGT GGA CTGTGCA GCCCATTTGT CTGCCCTGAGA AGGACTCCTG GACTGTGAAT  
20 GACATCCAGA AGCTGGTGGG CAAGCTGAAC TGGGCCTCCC AAATCTACCC TGGCATCAAG  
GTGAGGCAGC TGTGCAAGCT GCTGAGGGGC ACCAAGGCCC TGA CTGAGGT GATCCCCCTG  
ACTGAGGAGG CTGAGCTGGA GCTGGCTGAG AACAGGGAGA TCCTGAAGGA GCCTGTGCAT  
GGGGTGTA CT ATGACCCCTC CAAGGACCTG ATTGCTGAGA TCCAGAAGCA GGGCCAGGGC  
CAGTGGACCT ACCAAATCTA CCAGGAGCCC TTCAAGAAC TGAAGACTGG CAAGTATGCC  
25 AGGATGAGGG GGGCCACAC CAATGATGTG AAGCAGCTGA CTGAGGCTGT GCAGAAGATC  
ACCACTGAGT CCATTGTGAT CTGGGGCAAG ACCCCCAAGT TCAAGCTGCC CATCCAGAAG  
GAGACCTGGG AGACCTGGTG GACTGAGTAC TGGCAGGCCA CCTGGATCCC TGAGTGGGAG  
TTTGTGAACA CCCCCCCCCT GGTGAAGCTG TGGTACCAGC TGGAGAAGGA GCCCATTTGT  
GGGCTGAGA CCTTCTATGT GGCTGGGGCT GCCAACAGGG AGACCAAGCT GGGCAAGGCT  
30 GGCTATGTGA CCAACAGGGG CAGGCAGAAG GTGGTGACCC TGA CTGACAC CACCAACCAG  
AAGACTGCCC TCCAGGCCAT CTACCTGGCC CTCCAGGACT CTGGCCTGGA GGTGAACATT  
GTGACTGCCT CCCAGTATGC CCTGGGCATC ATCCAGGCC AGCCTGATCA GTCTGAGTCT  
GAGCTGGTGA ACCAGATCAT TGAGCAGCTG ATCAAGAAGG AGAAGGTGTA CCTGGCCTGG  
GTGCTGCCC ACAAGGGCAT TGGGGGCAAT GAGCAGGTGG ACAAGCTGGT GTCTGCTGGC  
35 ATCAGGAAGG TGCTGTTCTT GGATGGCATT GACAAGGCCC AGGATGAGCA TGAGAAGTAC  
CACTCCAAC TGGAGGGCTAT GGCCTCTGAC TTCAACCTGC CCCCTGTGGT GGCTAAGGAG

ATGTGGCCT CCTGTGACAA GTGCCAGCTG AAGGGGGAGG CCATGCATGG GCAGGTGGAC  
 TGCTCCCCTG GCATCTGGCA GCTGGCCTGC ACCCACCTGG AGGGCAAGGT GATCCTGGTG  
 GCTGTGCATG TGGCCTCCGG CTACATTGAG GCTGAGGTGA TCCCTGCTGA GACAGGCCAG  
 GAGACTGCCT ACTTCCTGCT GAAGCTGGCT GGCAGGTGGC CTGTGAAGAC CATCCACACT  
 5 GCCAATGGCT CCAACTTCAC TGGGGCCACA GTGAGGGCTG CCTGCTGGTG GGCTGGCATC  
 AAGCAGGAGT TTGGCATCCC CTACAACCCC CAGTCCCAGG GGGTGGTGGC CTCCATGAAC  
 AAGGAGCTGA AGAAGATCAT TGGGCAGGTG AGGGACCAGG CTGAGCACCT GAAGACAGCT  
 GTGCAGATGG CTGTGTTTCAT CCACAACCTC AAGAGGAAGG GGGGCATCGG GGGCTACTCC  
 GCTGGGGAGA GGATTGTGGA CATCATTGCC ACAGACATCC AGACCAAGGA GCTCCAGAAG  
 10 CAGATCACCA AGATCCAGAA CTTCAGGGTG TACTACAGGG ACTCCAGGAA CCCCCTGTGG  
 AAGGGCCCCTG CCAAGCTGCT GTGGAAGGGG GAGGGGGCTG TGGTGATCCA GGACAACCTCT  
 GACATCAAGG TGGTGGCCAG GAGGAAGGCC AAGATCATCA GGGACTATGG CAAGCAGATG  
 GCTGGGGATG ACTGTGTGGC CTCCAGGCAG GATGAGGACT AAAGCCCGGG CAGATCT (SEQ ID  
 NO:3).

- 15 In order to produce the IA-pol-based adenoviral vaccines of the present  
 invention, inactivation of the enzymatic functions was achieved by replacing a total of  
 nine active site residues from the enzyme subunits with alanine side-chains. As  
 shown in Table 1, all residues that comprise the catalytic triad of the polymerase,  
 namely Asp112, Asp187, and Asp188, were substituted with alanine (Ala) residues  
 20 (Larder, et al., *Nature* 1987, 327: 716-717; Larder, et al., 1989, *Proc. Natl. Acad. Sci.*  
 1989, 86: 4803-4807). Three additional mutations were introduced at Asp445,  
 Glu480 and Asp500 to abolish RNase H activity (Asp551 was left unchanged in this  
 IA Pol construct), with each residue being substituted for an Ala residue, respectively  
 (Davies, et al., 1991, *Science* 252:, 88-95; Schatz, et al., 1989, *FEBS Lett.* 257: 311-  
 25 314; Mizrahi, et al., 1990, *Nucl. Acids. Res.* 18: pp. 5359-5353). HIV pol integrase  
 function was abolished through three mutations at Asp626, Asp678 and Glu714.  
 Again, each of these residues has been substituted with an Ala residue (Wiskerchen,  
 et al., 1995, *J. Virol.* 69: 376-386; Leavitt, et al., 1993, *J. Biol. Chem.* 268: 2113-  
 2119). Amino acid residue Pro3 of SEQ ID NO:4 marks the start of the RT gene.  
 30 The complete amino acid sequence of IA-Pol is disclosed herein as SEQ ID NO:4 and  
 Figure 17A-C, as follows:

Met Ala Pro Ile Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro  
 Gly Met Asp Gly Pro Lys Val Lys Gln Trp Pro Leu Thr Glu Glu Lys  
 Ile Lys Ala Leu Val Glu Ile Cys Thr Glu Met Glu Lys Glu Gly Lys  
 35 Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr Asn Thr Pro Val Phe Ala  
 Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu Val Asp Phe Arg

Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu Gly Ile  
 Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Ala  
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys  
 Tyr Thr Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile  
 5 Arg Tyr Gln Tyr Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala  
 Ile Phe Gln Ser Ser Met Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln  
 Asn Pro Asp Ile Val Ile Tyr Gln Tyr Met Ala Ala Leu Tyr Val Gly  
 Ser Asp Leu Glu Ile Gly Gln His Arg Thr Lys Ile Glu Glu Leu Arg  
 Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp Lys Lys His Gln  
 10 Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro Asp Lys  
 Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val  
 Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile  
 Tyr Pro Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr  
 Lys Ala Leu Thr Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu  
 15 Leu Ala Glu Asn Arg Glu Ile Leu Lys Glu Pro Val His Gly Val Tyr  
 Tyr Asp Pro Ser Lys Asp Leu Ile Ala Glu Ile Gln Lys Gln Gly Gln  
 Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu Pro Phe Lys Asn Leu Lys  
 Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr Asn Asp Val Lys  
 Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile Val Ile  
 20 Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp  
 Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp  
 Glu Phe Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu  
 Lys Glu Pro Ile Val Gly Ala Glu Thr Phe Tyr Val Ala Gly Ala Ala  
 Asn Arg Glu Thr Lys Leu Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly  
 25 Arg Gln Lys Val Val Thr Leu Thr Asp Thr Thr Asn Gln Lys Thr Ala  
 Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp Ser Gly Leu Glu Val Asn  
 Ile Val Thr Ala Ser Gln Tyr Ala Leu Gly Ile Ile Gln Ala Gln Pro  
 Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln Leu Ile  
 Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile  
 30 Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys  
 Val Leu Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys  
 Tyr His Ser Asn Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro  
 Val Val Ala Lys Glu Ile Val Ala Ser Cys Asp Lys Cys Gln Leu Lys  
 Gly Glu Ala Met His Gly Gln Val Asp Cys Ser Pro Gly Ile Trp Gln  
 35 Leu Ala Cys Thr His Leu Glu Gly Lys Val Ile Leu Val Ala Val His  
 Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly

Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val  
 Lys Thr Ile His Thr Ala Asn Gly Ser Asn Phe Thr Gly Ala Thr Val  
 Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro  
 Tyr Asn Pro Gln Ser Gln Gly Val Val Ala Ser Met Asn Lys Glu Leu  
 5 Lys Lys Ile Ile Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr  
 Ala Val Gln Met Ala Val Phe Ile His Asn Phe Lys Arg Lys Gly Gly  
 Ile Gly Gly Tyr Ser Ala Gly Glu Arg Ile Val Asp Ile Ile Ala Thr  
 Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln Ile Thr Lys Ile Gln Asn  
 Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu Trp Lys Gly Pro  
 10 Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln Asp Asn  
 Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp  
 Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp  
 Glu Asp (SEQ ID NO:4).

As noted above, it will be understood that any combination of the mutations  
 15 disclosed above may be suitable and therefore be utilized as an IA-pol-based  
 adenoviral HIV vaccine of the present invention, either when administered alone or in  
 a combined modality regime and/or a prime-boost regimen. For example, it may be  
 possible to mutate only 2 of the 3 residues within the respective reverse transcriptase,  
 RNase-H, and integrase coding regions while still abolishing these enzymatic  
 20 activities. However, the IA-pol construct described above and disclosed as SEQ ID  
 NO:3, as well as the expressed protein (SEQ ID NO:4;) is preferred. It is also  
 preferred that at least one mutation be present in each of the three catalytic domains.

Another aspect of this portion of the invention are codon optimized HIV-1  
 Pol-based vaccine constructions which comprise a eukaryotic trafficking signal  
 25 peptide such as from tPA (tissue-type plasminogen activator) or by a leader peptide  
 such as is found in highly expressed mammalian proteins such as immunoglobulin  
 leader peptides. Any functional leader peptide may be tested for efficacy. However,  
 a preferred embodiment of the present invention, as with HIV-1 Nef constructs shown  
 herein, is to provide for a HIV-1 Pol mutant adenoviral vaccine construction wherein  
 30 the pol coding region or a portion thereof is operatively linked to a leader peptide,  
 preferably a leader peptide from human tPA. In other words, a codon optimized  
 HIV-1 Pol mutant such as IA-Pol (SEQ ID NO:4) may also comprise a leader peptide  
 at the amino terminal portion of the protein, which may effect cellular trafficking and  
 hence, immunogenicity of the expressed protein within the host cell. As noted in  
 35 Figure 16A-B, a DNA vector which may be utilized to practice the present invention  
 may be modified by known recombinant DNA methodology to contain a leader signal

peptide of interest, such that downstream cloning of the modified HIV-1 protein of interest results in a nucleotide sequence which encodes a modified HIV-1 tPA/Pol protein. In the alternative, as noted above, insertion of a nucleotide sequence which encodes a leader peptide may be inserted into a DNA vector housing the open reading frame for the Pol protein of interest. Regardless of the cloning strategy, the end result is a polynucleotide vaccine which comprises vector components for effective gene expression in conjunction with nucleotide sequences which encode a modified HIV-1 Pol protein of interest, including but not limited to a HIV-1 Pol protein which contains a leader peptide. The amino acid sequence of the human tPA leader utilized herein is as follows: MDAMKRGLCCVLLLCGAVFVSPSEISS (SEQ ID NO:17). Therefore, another aspect of the present invention is to generate HIV-1 Pol-based vaccine constructions which comprise a eukaryotic trafficking signal peptide such as from tPA. To this end, the present invention relates to a DNA molecule which encodes a codon optimized wt-pol DNA construct wherein the protease (PR) activity is deleted and a human tPA leader sequence is fused to the 5' end of the coding region. A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:5, the open reading frame disclosed herein as SEQ ID NO:6.

To this end, the present invention relates to a DNA molecule which encodes a codon optimized wt-pol DNA construct wherein the protease (PR) activity is deleted and a human tPA leader sequence is fused to the 5' end of the coding region ( herein, "tPA-wt-pol"). A DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:5, the open reading frame being contained from an initiating Met residue at nucleotides 8-10 to a termination codon from nucleotides 2633-2635. SEQ ID NO:5 is as follows:

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25  GATCACCATG GATGCAATGA AGAGAGGGCT CTGCTGTGTG CTGCTGCTGT GTGGAGCAGT
    CTTCTGTTTCG CCCAGCGAGA TCTCCGCCCC CATCTCCCCC ATTGAGACTG TGCTGTGAA
    GCTGAAGCCT GGCATGGATG GCCCCAAGGT GAAGCAGTGG CCCCTGACTG AGGAGAAGAT
    CAAGGCCCTG GTGGAAATCT GCACTGAGAT GGAGAAGGAG GGCAAAATCT CCAAGATTGG
    CCCCAGAGAAC CCCTACAACA CCCCTGTGTT TGCCATCAAG AAGAAGGACT CCACCAAGTG
30  GAGGAAGCTG GTGGACTTCA GGGAGCTGAA CAAGAGGACC CAGGACTTCT GGGAGGTGCA
    GCTGGGCATC CCCCACCCCG CTGGCCTGAA GAAGAAGAAG TCTGTGACTG TGCTGGATGT
    GGGGGATGCC TACTTCTCTG TGCCCTGGA TGAGGACTTC AGGAAGTACA CTGCCTTCAC
    CATCCCCTCC ATCAACAATG AGACCCCTGG CATCAGGTAC CAGTACAATG TGCTGCCCCA
    GGGCTGGAAG GGCTCCCTCG CCATCTTCCA GTCCTCCATG ACCAAGATCC TGGAGCCCTT
35  CAGGAAGCAG AACCTTGACA TTGTGATCTA CCAGTACATG GATGACCTGT ATGTGGGCTC
    TGACCTGGAG ATTGGGCAGC ACAGGACCAA GATTGAGGAG CTGAGGCAGC ACCTGCTGAG

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GTGGGGCCTG ACCACCCCTG ACAAGAAGCA CCAGAAGGAG CCCCCCTTCC TGTGGATGGG  
 CTATGAGCTG CACCCCGACA AGTGGACTGT GCAGCCCAT TGTGCTGCCTG AGAAGGACTC  
 CTGGACTGTG AATGACATCC AGAAGCTGGT GGGCAAGCTG AACTGGGCCT CCCAAATCTA  
 CCCTGGCATC AAGGTGAGGC AGCTGTGCAA GCTGCTGAGG GGCACCAAGG CCCTGACTGA  
 5 GGTGATCCCC CTGACTGAGG AGGCTGAGCT GGAGCTGGCT GAGAACAGGG AGATCCTGAA  
 GGAGCCTGTG CATGGGGTGT ACTATGACCC CTCCAAGGAC CTGATTGCTG AGATCCAGAA  
 GCAGGGCCAG GGCCAGTGA CCTACCAAAT CTACCAGGAG CCCTTCAAGA ACCTGAAGAC  
 TGGCAAGTAT GCCAGGATGA GGGGGGCCA CACCAATGAT GTGAAGCAGC TGACTGAGGC  
 TGTGCAGAAG ATCACCCTG AGTCCATTGT GATCTGGGGC AAGACCCCCA AGTTCAAGCT  
 10 GCCCATCCAG AAGGAGACCT GGGAGACCTG GTGGACTGAG TACTGGCAGG CCACCTGGAT  
 CCCTGAGTGG GAGTTTGTGA ACACCCCCC CTGGTGAAG CTGTGGTACC AGCTGGAGAA  
 GGAGCCCAT GTGGGGCTG AGACCTTCTA TGTGGATGGG GCTGCCAACA GGGAGACCAA  
 GCTGGGCAAG GCTGGCTATG TGACCAACAG GGCAGGCAG AAGTGGTGA CCCTGACTGA  
 CACCACCAAC CAGAAGACTG AGTCCAGGC CATCTACCTG GCCCTCCAGG ACTCTGGCCT  
 15 GGAGGTGAAC ATTGTGACTG ACTCCCAGTA TGCCCTGGGC ATCATCCAGG CCCAGCCTGA  
 TCAGTCTGAG TCTGAGCTGG TGAACCAGAT CATTGAGCAG CTGATCAAGA AGGAGAAGGT  
 GTACCTGGCC TGGGTGCCTG CCCACAAGGG CATTGGGGGC AATGAGCAGG TGGACAAGCT  
 GGTGTCTGCT GGCATCAGGA AGGTGCTGTT CCTGGATGGC ATTGACAAGG CCCAGGATGA  
 GCATGAGAAG TACCACTCCA ACTGGAGGGC TATGGCCTCT GACTTCAACC TGCCCCCTGT  
 20 GGTGGCTAAG GAGATTGTGG CCTCCTGTGA CAAGTGCCAG CTGAAGGGGG AGGCCATGCA  
 TGGGCAGGTG GACTGCTCCC CTGGCATCTG GCAGCTGGAC TGCACCCACC TGGAGGGCAA  
 GGTGATCCTG GTGGCTGTGC ATGTGGCCTC CGGCTACATT GAGGCTGAGG TGATCCCTGC  
 TGAGACAGGC CAGGAGACTG CCTACTTCCT GCTGAAGCTG GCTGGCAGGT GGCCTGTGAA  
 GACCATCCAC ACTGACAATG GCTCCAACCT CACTGGGGCC ACAGTGAGGG CTGCCTGCTG  
 25 GTGGGCTGGC ATCAAGCAGG AGTTTGGCAT CCCCTACAAC CCCCAGTCCC AGGGGGTGGT  
 GGAGTCCATG AACAAGGAGC TGAAGAAGAT CATTGGGCAG GTGAGGGACC AGGCTGAGCA  
 CCTGAAGACA GCTGTGCAGA TGGCTGTGTT CATCCACAAC TTCAAGAGGA AGGGGGGCAT  
 CGGGGGCTAC TCCGCTGGGG AGAGGATTGT GGACATCATT GCCACAGACA TCCAGACCAA  
 GGAGCTCCAG AAGCAGATCA CCAAGATCCA GAACTTCAGG GTGTACTACA GGGACTCCAG  
 30 GAACCCCTG TGAAGGGGCC CTGCCAAGCT GCTGTGGAAG GGGGAGGGGG CTGTGGTGAT  
 CCAGGACAACT TCTGACATCA AGGTGGTGCC CAGGAGGAAG GCCAAGATCA TCAGGGACTA  
 TGGCAAGCAG ATGGCTGGGG ATGACTGTGT GGCCTCCAGG CAGGATGAGG ACTAAAGCCC  
 GGGCAGATCT (SEQ ID NO:5).

The open reading frame of the wild type tPA-pol construct disclosed as SEQ

35 ID NO:5 contains 875 amino acids, disclosed herein as SEQ ID NO:6, as follows:

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly

Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ala Pro Ile Ser Pro Ile  
 Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys Val  
 Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile  
 Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu  
 5 Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr  
 Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln  
 Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His Pro Ala Gly Leu Lys  
 Lys Lys Lys Ser Val Thr Val Leu Asp Val Gly Asp Ala Tyr Phe Ser  
 Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr Ala Phe Thr Ile Pro  
 10 Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr Asn Val Leu  
 Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met Thr  
 Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr  
 Gln Tyr Met Asp Asp Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln  
 His Arg Thr Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly  
 15 Leu Thr Thr Pro Asp Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp  
 Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr Val Gln Pro Ile Val  
 Leu Pro Glu Lys Asp Ser Trp Thr Val Asn Asp Ile Gln Lys Leu Val  
 Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro Gly Ile Lys Val Arg  
 Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr Glu Val Ile  
 20 Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu Ile  
 Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu  
 Ile Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile  
 Tyr Gln Glu Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met  
 Arg Gly Ala His Thr Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln  
 25 Lys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Lys Thr Pro Lys Phe  
 Lys Leu Pro Ile Gln Lys Glu Thr Trp Glu Thr Trp Trp Thr Glu Tyr  
 Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr Pro Pro  
 Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile Val Gly Ala  
 Glu Thr Phe Tyr Val Asp Gly Ala Ala Asn Arg Glu Thr Lys Leu Gly  
 30 Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu  
 Thr Asp Thr Thr Asn Gln Lys Thr Glu Leu Gln Ala Ile Tyr Leu Ala  
 Leu Gln Asp Ser Gly Leu Glu Val Asn Ile Val Thr Asp Ser Gln Tyr  
 Ala Leu Gly Ile Ile Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu  
 Val Asn Gln Ile Ile Glu Gln Leu Ile Lys Lys Glu Lys Val Tyr Leu  
 35 Ala Trp Val Pro Ala His Lys Gly Ile Gly Gly Asn Glu Gln Val Asp  
 Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu Phe Leu Asp Gly Ile

Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn Trp Arg Ala  
 Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile Val  
 Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln  
 Val Asp Cys Ser Pro Gly Ile Trp Gln Leu Asp Cys Thr His Leu Glu  
 5 Gly Lys Val Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu  
 Ala Glu Val Ile Pro Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu  
 Leu Lys Leu Ala Gly Arg Trp Pro Val Lys Thr Ile His Thr Asp Asn  
 Gly Ser Asn Phe Thr Gly Ala Thr Val Arg Ala Ala Cys Trp Trp Ala  
 Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn Pro Gln Ser Gln Gly  
 10 Val Val Glu Ser Met Asn Lys Glu Leu Lys Lys Ile Ile Gly Gln Val  
 Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val Phe  
 Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly  
 Glu Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu  
 Gln Lys Gln Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp  
 15 Ser Arg Asn Pro Leu Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly  
 Glu Gly Ala Val Val Ile Gln Asp Asn Ser Asp Ile Lys Val Val Pro  
 Arg Arg Lys Ala Lys Ile Ile Arg Asp Tyr Gly Lys Gln Met Ala Gly  
 Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp (SEQ ID NO:6).

The present invention also relates to a codon optimized HIV-1 Pol mutant  
 20 contained within a recombinant adenoviral vector such as IA-Pol (SEQ ID NO:4)  
 which comprises a leader peptide at the amino terminal portion of the protein, which  
 may effect cellular trafficking and hence, immunogenicity of the expressed protein  
 within the host cell. Any such adenoviral-based HIV-1 DNA pol mutant disclosed in  
 the above paragraphs is suitable for fusion downstream of a leader peptide, such as a  
 25 leader peptide including but not limited to the human tPA leader sequence. Therefore,  
 any such leader peptide-based HIV-1 pol mutant construct may include but is not  
 limited to a mutated DNA molecule which effectively alters the catalytic activity of  
 the RT, RNase and/or IN region of the expressed protein, resulting in at least  
 substantially decreased enzymatic activity one or more of the RT, RNase H and/or IN  
 30 functions of HIV-1 Pol. In a preferred embodiment of this portion of the invention, a  
 leader peptide/HIV-1 DNA pol construct contains a mutation or mutations within the  
 Pol coding region which effectively abolishes RT, RNase H and IN activity. An  
 especially preferable HIV-1 DNA pol construct is a DNA molecule which contains at  
 least one point mutation which alters the active site and catalytic activity within the  
 35 RT, RNase H and IN domains of Pol, such that each activity is at least substantially  
 abolished, and preferably totally abolished. Such a HIV-1 Pol mutant will most likely

comprise at least one point mutation in or around each catalytic domain responsible for RT, RNase H and IN activity, respectfully. An especially preferred embodiment of this portion of the invention relates to a human tPA leader fused to the IA-Pol protein comprising the nine mutations shown in Table 1. The DNA molecule is disclosed  
 5 herein as SEQ ID NO:7 and the expressed tPA-IA Pol protein comprises a fusion junction as shown in Figure 18. The complete amino acid sequence of the expressed protein is set forth in SEQ ID NO:8. To this end, SEQ ID NO:7 discloses the nucleotide sequence which codes for a human tPA leader fused to the IA Pol protein comprising the nine mutations shown in Table 1 (herein, "tPA-opt-IApol"). The open  
 10 reading frame begins with the initiating Met (nucleotides 8-10) and terminates with a "TAA" codon at nucleotides 2633-2635. The nucleotide sequence encoding tPA-IAPol is also disclosed as follows:

GATCACCATG GATGCAATGA AGAGAGGGCT CTGCTGTGTG CTGCTGCTGT GTGGAGCAGT  
 CTTTCGTTTCG CCCAGCGAGA TCTCCGCCCC CATCTCCCCC ATTGAGACTG TGCCTGTGAA  
 15 GCTGAAGCCT GGCATGGATG GCCCAAGGT GAAGCAGTGG CCCCTGACTG AGGAGAAGAT  
 CAAGGCCCTG GTGGAAATCT GCACTGAGAT GGAGAAGGAG GGCAAAATCT CCAAGATTGG  
 CCCCAGAAC CCCTACAACA CCCCTGTGTT TGCCATCAAG AAGAAGGACT CCACCAAGTG  
 GAGGAAGCTG GTGGACTTCA GGGAGCTGAA CAAGAGGACC CAGGACTTCT GGGAGGTGCA  
 GCTGGGCATC CCCCACCCCG CTGGCCTGAA GAAGAAGAAG TCTGTGACTG TGCTGGCTGT  
 20 GGGGGATGCC TACTTCTCTG TGCCCTGGA TGAGGACTTC AGGAAGTACA CTGCCTTCAC  
 CATCCCTCC ATCAACAATG AGACCCCTGG CATCAGGTAC CAGTACAATG TGCTGCCCCA  
 GGGCTGGAAG GGCTCCCTG CCATCTTCCA GTCCTCCATG ACCAAGATCC TGGAGCCCTT  
 CAGGAAGCAG AACCTGACA TTGTGATCTA CCAGTACATG GCTGCCCTGT ATGTGGGCTC  
 TGACCTGGAG ATTGGGCAGC ACAGGACCAA GATTGAGGAG CTGAGGCAGC ACCTGCTGAG  
 25 GTGGGGCCTG ACCACCCCTG ACAAGAAGCA CCAGAAGGAG CCCCCTTCC TGTGGATGGG  
 CTATGAGCTG CACCCGACA AGTGGACTGT GCAGCCCAT GTGCTGCCTG AGAAGGACTC  
 CTGGACTGTG AATGACATCC AGAAGCTGGT GGGCAAGCTG AACTGGGCCT CCCAAATCTA  
 CCCTGGCATC AAGGTGAGGC AGCTGTGCAA GCTGCTGAGG GGCACCAAGG CCCTGACTGA  
 GGTGATCCCC CTGACTGAGG AGGCTGAGCT GGAGCTGGCT GAGAACAGGG AGATCCTGAA  
 30 GGAGCCTGTG CATGGGGTGT ACTATGACCC CTCCAAGGAC CTGATTGCTG AGATCCAGAA  
 GCAGGGCCAG GGCCAGTGGA CCTACCAAAT CTACCAGGAG CCCTTCAAGA ACCTGAAGAC  
 TGGCAAGTAT GCCAGGATGA GGGGGGCCCA CACCAATGAT GTGAAGCAGC TGA CTGAGGC  
 TGTGCAGAAG ATCACCCTG AGTCCATTGT GATCTGGGGC AAGACCCCCA AGTTCAAGCT  
 GCCCATCCAG AAGGAGACCT GGGAGACCTG GTGGACTGAG TACTGGCAGG CCACCTGGAT  
 35 CCCTGAGTGG GAGTTTGTGA ACACCCCCC CCTGGTGAAG CTGTGGTACC AGCTGGAGAA  
 GGAGCCCAT GTGGGGGCTG AGACCTTCTA TGTGGCTGGG GCTGCCAACA GGGAGACCAA

GCTGGGCAAG GCTGGCTATG TGACCAACAG GGGCAGGCAG AAGGTGGTGA CCCTGACTGA  
 CACCACCAAC CAGAAGACTG CCCTCCAGGC CATCTACCTG GCCCTCCAGG ACTCTGGCCT  
 GGAGGTGAAC ATTGTGACTG CCTCCAGTA TGCCCTGGGC ATCATCCAGG CCCAGCCTGA  
 TCAGTCTGAG TCTGAGCTGG TGAACCAGAT CATTGAGCAG CTGATCAAGA AGGAGAAGGT  
 5 GTACCTGGCC TGGGTGCCCTG CCCACAAGGG CATTGGGGGC AATGAGCAGG TGGACAAGCT  
 GGTGTCTGCT GGCATCAGGA AGGTGCTGTT CCTGGATGGC ATTGACAAGG CCCAGGATGA  
 GCATGAGAAG TACCACTCCA ACTGGAGGGC TATGGCCTCT GACTTCAACC TGCCCCCTGT  
 GGTGGCTAAG GAGATTGTGG CCTCCTGTGA CAAGTGCCAG CTGAAGGGGG AGGCCATGCA  
 TGGGCAGGTG GACTGCTCCC CTGGCATCTG GCAGCTGGCC TGCACCCACC TGGAGGGCAA  
 10 GGTGATCCTG GTGGCTGTGC ATGTGGCCTC CGGCTACATT GAGGCTGAGG TGATCCCTGC  
 TGAGACAGGC CAGGAGACTG CCTACTTCCT GCTGAAGCTG GCTGGCAGGT GGCCTGTGAA  
 GACCATCCAC ACTGCCAATG GCTCCAACCT CACTGGGGCC ACAGTGAGGG CTGCCTGCTG  
 GTGGGCTGGC ATCAAGCAGG AGTTTGGCAT CCCCTACAAC CCCCAGTCCC AGGGGGTGGT  
 GGCCTCCATG AACAAGGAGC TGAAGAAGAT CATTGGGCAG GTGAGGGACC AGGCTGAGCA  
 15 CCTGAAGACA GCTGTGCAGA TGGCTGTGTT CATCCACAAC TTCAAGAGGA AGGGGGGCAT  
 CGGGGGCTAC TCCGCTGGGG AGAGGATTGT GGACATCATT GCCACAGACA TCCAGACCAA  
 GGAGCTCCAG AAGCAGATCA CCAAGATCCA GAACTTCAGG GTGTACTACA GGGACTCCAG  
 GAACCCCTG TGAAGGGGCC CTGCCAAGCT GCTGTGGAAG GGGGAGGGGG CTGTGGTGTAT  
 CCAGGACAAC TCTGACATCA AGGTGGTGCC CAGGAGGAAG GCCAAGATCA TCAGGGACTA  
 20 TGGCAAGCAG ATGGCTGGGG ATGACTGTGT GGCCTCCAGG CAGGATGAGG ACTAAAGCCC  
 GGGCAGATCT (SEQ ID NO:7).

The open reading frame of the tPA-IA-pol construct disclosed as SEQ ID NO:7 contains 875 amino acids, disclosed herein as tPA-IA-Pol and SEQ ID NO:8, as follows:

25 Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly  
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ala Pro Ile Ser Pro Ile  
 Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys Val  
 Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile  
 Cys Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu  
 30 Asn Pro Tyr Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr  
 Lys Trp Arg Lys Leu Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln  
 Asp Phe Trp Glu Val Gln Leu Gly Ile Pro His Pro Ala Gly Leu Lys  
 Lys Lys Lys Ser Val Thr Val Leu Ala Val Gly Asp Ala Tyr Phe Ser  
 Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr Ala Phe Thr Ile Pro  
 35 Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr Asn Val Leu  
 Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met Thr

Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr  
 Gln Tyr Met Ala Ala Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln  
 His Arg Thr Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly  
 Leu Thr Thr Pro Asp Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp  
 5 Met Gly Tyr Glu Leu His Pro Asp Lys Trp Thr Val Gln Pro Ile Val  
 Leu Pro Glu Lys Asp Ser Trp Thr Val Asn Asp Ile Gln Lys Leu Val  
 Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro Gly Ile Lys Val Arg  
 Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr Glu Val Ile  
 Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu Ile  
 10 Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu  
 Ile Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile  
 Tyr Gln Glu Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met  
 Arg Gly Ala His Thr Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln  
 Lys Ile Thr Thr Glu Ser Ile Val Ile Trp Gly Lys Thr Pro Lys Phe  
 15 Lys Leu Pro Ile Gln Lys Glu Thr Trp Glu Thr Trp Trp Thr Glu Tyr  
 Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe Val Asn Thr Pro Pro  
 Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile Val Gly Ala  
 Glu Thr Phe Tyr Val Ala Gly Ala Ala Asn Arg Glu Thr Lys Leu Gly  
 Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu  
 20 Thr Asp Thr Thr Asn Gln Lys Thr Ala Leu Gln Ala Ile Tyr Leu Ala  
 Leu Gln Asp Ser Gly Leu Glu Val Asn Ile Val Thr Ala Ser Gln Tyr  
 Ala Leu Gly Ile Ile Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu  
 Val Asn Gln Ile Ile Glu Gln Leu Ile Lys Lys Glu Lys Val Tyr Leu  
 Ala Trp Val Pro Ala His Lys Gly Ile Gly Gly Asn Glu Gln Val Asp  
 25 Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu Phe Leu Asp Gly Ile  
 Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn Trp Arg Ala  
 Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile Val  
 Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln  
 Val Asp Cys Ser Pro Gly Ile Trp Gln Leu Ala Cys Thr His Leu Glu  
 30 Gly Lys Val Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu  
 Ala Glu Val Ile Pro Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu  
 Leu Lys Leu Ala Gly Arg Trp Pro Val Lys Thr Ile His Thr Ala Asn  
 Gly Ser Asn Phe Thr Gly Ala Thr Val Arg Ala Ala Cys Trp Trp Ala  
 Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn Pro Gln Ser Gln Gly  
 35 Val Val Ala Ser Met Asn Lys Glu Leu Lys Lys Ile Ile Gly Gln Val  
 Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val Phe

Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly  
 Glu Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu  
 Gln Lys Gln Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp  
 Ser Arg Asn Pro Leu Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly  
 5 Glu Gly Ala Val Val Ile Gln Asp Asn Ser Asp Ile Lys Val Val Pro  
 Arg Arg Lys Ala Lys Ile Ile Arg Asp Tyr Gly Lys Gln Met Ala Gly  
 Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp (SEQ ID NO:8).

### EXAMPLE 18

#### 10 CODON OPTIMIZED HIV-1 NEF AND CODON OPTIMIZED HIV-1 NEF MODIFICATIONS

Codon optimized version of HIV-1 Nef and HIV-1 Nef modifications are essentially as described in U.S. Application Serial No. 09/738,782, filed December 15, 2000 and PCT International Application PCT/US00/34162, also filed  
 15 December 15, 2000, both documents which are hereby incorporated by reference. As disclosed within the above-mentioned documents, particular embodiments of codon optimized Nef and Nef modifications relate to a DNA molecule encoding HIV-1 Nef from the HIV-1 jf1 isolate wherein the codons are optimized for expression in a mammalian system such as a human. The DNA molecule which encodes this protein  
 20 is disclosed herein as SEQ ID NO:9, while the expressed open reading frame is disclosed herein as SEQ ID NO:10. Another embodiment of Nef-based coding regions for use in the adenoviral vectors of the present invention comprise a codon optimized DNA molecule encoding a protein containing the human plasminogen activator (tpa) leader peptide fused with the NH<sub>2</sub>-terminus of the HIV-1 Nef  
 25 polypeptide. The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:11, while the expressed open reading frame is disclosed herein as SEQ ID NO:12. Another modified Nef optimized coding region relates to a DNA molecule encoding optimized HIV-1 Nef wherein the open reading frame codes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and  
 30 substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175, herein described as opt nef (G2A, LLAA). The DNA molecule which encodes this protein is disclosed herein as SEQ ID NO:13, while the expressed open reading frame is disclosed herein as SEQ ID NO:14. An additional embodiment relates to a DNA molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation  
 35 site and dileucine motif have been deleted, as well as comprising a tPA leader peptide. This DNA molecule, opt tpanef (LLAA), comprises an open reading frame which

encodes a Nef protein containing a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef (jfr1), wherein Leu-174 and Leu-175 are substituted with Ala-174 and Ala-175, herein referred to as opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, while the expressed open reading frame is disclosed herein as SEQ ID NO:16.

5 As disclosed in the above-identified documents (U.S. Application Serial No. 09/738,782 and PCT International Application PCT/US00/34162) and reiterated herein, the following nef-based nucleotide and amino acid sequences which comprise the respective open reading frame are as follows:

1. The nucleotide sequence of the codon optimized version of HIV-1 jfr1  
10 nef gene is disclosed herein as SEQ ID NO:9, as shown herein:

GATCTGCCAC CATGGGCGGC AAGTGGTCCA AGAGGTCCGT GCCCGGCTGG TCCACCGTGA  
GGGAGAGGAT GAGGAGGGCC GAGCCCGCCG CCGACAGGGT GAGGAGGACC GAGCCCGCCG  
CCGTGGGCGT GGGCGCCGTG TCCAGGGACC TGGAGAAGCA CGGCGCCATC ACCTCCTCCA  
ACACCGCCGC CACCAACGCC GACTGCGCCT GGCTGGAGGC CCAGGAGGAC GAGGAGGTGG  
15 GCTTCCCCGT GAGGCCCCAG GTGCCCTTGA GGCCCATGAC CTACAAGGGC GCCGTGGACC  
TGTCCCCTT CCTGAAGGAG AAGGGCGGCC TGGAGGGCCT GATCCACTCC CAGAAGAGGC  
AGGACATCCT GGACCTGTGG GTGTACCACA CCCAGGGCTA CTTCCCCGAC TGGCAGAACT  
ACACCCCCGG CCCCGGCATC AGGTTCCCCC TGACCTTCGG CTGGTGCTTC AAGCTGGTGC  
CCGTGGAGCC CGAGAAGGTG GAGGAGGCCA ACGAGGGCGA GAACAACATGC CTGCTGCACC  
20 CCATGTCCCA GCACGGCATC GAGGACCCCG AGAAGGAGGT GCTGGAGTGG AGGTTGCACT  
CCAAGCTGGC CTTCCACCAC GTGGCCAGGG AGCTGCACCC CGAGTACTAC AAGGACTGCT  
AAAGCCCCGG C (SEQ ID NO:9).

Preferred codon usage is as follows: Met (ATG), Gly (GGC), Lys (AAG),  
Trp (TGG), Ser (TCC), Arg (AGG), Val (GTG), Pro (CCC), Thr (ACC), Glu (GAG);  
25 Leu (CTG), His (CAC), Ile (ATC), Asn (AAC), Cys (TGC), Ala (GCC), Gln (CAG),  
Phe (TTC) and Tyr (TAC). For an additional discussion relating to mammalian  
(human) codon optimization, see WO 97/31115 (PCT/US97/02294), which is hereby  
incorporated by reference. See also Figure 19A-B for a comparison of wild type vs.  
codon optimized nucleotides comprising the open reading frame of HIV-Nef.

30 The open reading frame for SEQ ID NO:9 above comprises an initiating  
methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides  
660-662. The open reading frame of SEQ ID NO:9 provides for a 216 amino acid  
HIV-1 Nef protein expressed through utilization of a codon optimized DNA vaccine  
vector. The 216 amino acid HIV-1 Nef (jfr1) protein is disclosed herein as SEQ ID  
35 NO:10, and as follows:

Met Gly Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val

Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala Asp Arg Val Arg Arg  
 Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val Ser Arg Asp Leu Glu  
 Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala Ala Thr Asn Ala Asp  
 Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu Val Gly Phe Pro Val  
 5 Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr Lys Gly Ala Val Asp  
 Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu Glu Gly Leu Ile His  
 Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp Val Tyr His Thr Gln  
 Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly Ile Arg  
 Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu Val Pro Val Glu Pro  
 10 Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn Asn Cys Leu Leu His  
 Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu Lys Glu Val Leu Glu  
 Trp Arg Phe Asp Ser Lys Leu Ala Phe His His Val Ala Arg Glu Leu  
 His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:10).

HIV-1 Nef is a 216 amino acid cytosolic protein which associates with the  
 15 inner surface of the host cell plasma membrane through myristylation of Gly-2  
 (Franchini et al., 1986, *Virology* 155: 593-599). While not all possible Nef functions  
 have been elucidated, it has become clear that correct trafficking of Nef to the inner  
 plasma membrane promotes viral replication by altering the host intracellular  
 environment to facilitate the early phase of the HIV-1 life cycle and by increasing the  
 20 infectivity of progeny viral particles. In one aspect of the invention regarding  
 codon-optimized, protein-modified polypeptides, the nef-encoding region of the  
 adenovirus vector of the present invention is modified to contain a nucleotide  
 sequence which encodes a heterologous leader peptide such that the amino terminal  
 region of the expressed protein will contain the leader peptide. The diversity of  
 25 function that typifies eukaryotic cells depends upon the structural differentiation of  
 their membrane boundaries. To generate and maintain these structures, proteins must  
 be transported from their site of synthesis in the endoplasmic reticulum to  
 predetermined destinations throughout the cell. This requires that the trafficking  
 proteins display sorting signals that are recognized by the molecular machinery  
 30 responsible for route selection located at the access points to the main trafficking  
 pathways. Sorting decisions for most proteins need to be made only once as they  
 traverse their biosynthetic pathways since their final destination, the cellular location  
 at which they perform their function, becomes their permanent residence.  
 Maintenance of intracellular integrity depends in part on the selective sorting and  
 35 accurate transport of proteins to their correct destinations. Defined sequence motifs  
 exist in proteins which can act as 'address labels'. A number of sorting signals have

been found associated with the cytoplasmic domains of membrane proteins. An effective induction of CTL responses often required sustained, high level endogenous expression of an antigen. As membrane-association via myristylation is an essential requirement for most of Nef's function, mutants lacking myristylation, by glycine-to-  
5 alanine change, change of the dileucine motif and/or by substitution with a tpa leader sequence as described herein, will be functionally defective, and therefore will have improved safety profile compared to wild-type Nef for use as an HIV-1 vaccine component.

In another embodiment of this portion of the invention, either the DNA vector  
10 or the HIV-1 nef nucleotide sequence is modified to include the human tissue-specific plasminogen activator (tPA) leader. As shown in Figure 16A-B, a DNA vector may be modified by known recombinant DNA methodology to contain a leader signal peptide of interest, such that downstream cloning of the modified HIV-1 protein of interest results in a nucleotide sequence which encodes a modified HIV-1 tPA/Nef  
15 protein. In the alternative, as noted above, insertion of a nucleotide sequence which encodes a leader peptide may be inserted into a DNA vector housing the open reading frame for the Nef protein of interest. Regardless of the cloning strategy, the end result is a polynucleotide vaccine which comprises vector components for effective gene expression in conjunction with nucleotide sequences which encode a modified HIV-1  
20 Nef protein of interest, including but not limited to a HIV-1 Nef protein which contains a leader peptide. The amino acid sequence of the human tPA leader utilized herein is as follows: MDAMKRGLCCVLLLCGAVFVSPSEISS (SEQ ID NO:17).

It has been shown that myristylation of Gly-2 in conjunction with a dileucine motif in the carboxy region of the protein is essential for Nef-induced down  
25 regulation of CD4 (Aiken et al., 1994, *Cell* 76: 853-864) via endocytosis. It has also been shown that Nef expression promotes down regulation of MHCI (Schwartz et al., 1996, *Nature Medicine* 2(3): 338-342) via endocytosis. The present invention relates in part to DNA vaccines which encode modified Nef proteins altered in trafficking and/or functional properties. The modifications introduced into the adenoviral vector  
30 HIV vaccines of the present invention include but are not limited to additions, deletions or substitutions to the nef open reading frame which results in the expression of a modified Nef protein which includes an amino terminal leader peptide, modification or deletion of the amino terminal myristylation site, and modification or deletion of the dileucine motif within the Nef protein and which alter  
35 function within the infected host cell. Therefore, a central theme of the DNA molecules and recombinant adenoviral HIV vaccines of the present invention is (1)

host administration and intracellular delivery of a codon optimized nef-based adenoviral HIV vaccine; (2) expression of a modified Nef protein which is immunogenic in terms of eliciting both CTL and Th responses; and, (3) inhibiting or at least altering known early viral functions of Nef which have been shown to promote HIV-1 replication and load within an infected host. Therefore, the nef coding region may be altered, resulting in a DNA vaccine which expresses a modified Nef protein wherein the amino terminal Gly-2 myristylation residue is either deleted or modified to express alternate amino acid residues. Also, the nef coding region may be altered so as to result in a DNA vaccine which expresses a modified Nef protein wherein the dileucine motif is either deleted or modified to express alternate amino acid residues. In addition, the adenoviral vector HIV vaccines of the present invention also relate to an isolated DNA molecule, regardless of codon usage, which expresses a wild type or modified Nef protein as described herein, including but not limited to modified Nef proteins which comprise a deletion or substitution of Gly 2, a deletion or substitution of Leu 174 and Leu 175 and/or inclusion of a leader sequence.

Therefore, specific Nef-based constructs further include the following, as exemplification's and not limitations. For example, the present invention relates to an adenoviral vector vaccine which encodes modified forms of HIV-1, an open reading frame which encodes a Nef protein which comprises a tPA leader sequence fused to amino acid residue 6-216 of HIV-1 Nef (jfrl) is referred to herein as opt tpanef. The nucleotide sequence comprising the open reading frame of opt tpanef is disclosed herein as SEQ ID NO:11, as shown below:

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CATGGATGCA ATGAAGAGAG GGCTCTGCTG TGTGCTGCTG CTGTGTGGAG CAGTCTTCGT
TTCGCCCCAGC GAGATCTCCT CCAAGAGGTC CGTGCCCGGC TGGTCCACCG TGAGGGAGAG
GATGAGGAGG GCCGAGCCCC CCGCCGACAG GGTGAGGAGG ACCGAGCCCC CCGCCGTGGG
CGTGGGCGCC GTGTCCAGGG ACCTGGAGAA GCACGGCGCC ATCACCTCCT CCAACACCGC
CGCCACCAAC GCCGACTGCG CCTGGCTGGA GGCCCAAGAG GACGAGGAGG TGGGCTTCCC
CGTGAGGCCC CAGGTGCCCC TGAGGCCCAT GACCTACAAG GGCGCCGTGG ACCTGTCCCA
CTTCTGAAG GAGAAGGGCG GCCTGGAGGG CCTGATCCAC TCCCAGAAGA GGCAGGACAT
CCTGGACCTG TGGGTGTACC ACACCCAGGG CTACTTCCCC GACTGGCAGA ACTACACCCC
CGGCCCCGGC ATCAGGTTCC CCCTGACCTT CGGCTGGTGC TTCAAGCTGG TGCCCGTGGA
GCCCCAGAAG GTGGAGGAGG CCAACGAGGG CGAGAACAAC TGCCCTGCTGC ACCCATGTC
CCAGCACGGC ATCAGGAGCC CCGAGAAGGA GGTGCTGGAG TGGAGGTTTC ACTCCAAGCT
GGCCTTCCAC CACGTGGCCA GGGAGCTGCA CCCCAGTAC TACAAGGACT GCTAAAGCC

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(SEQ ID NO:11).

The open reading frame for SEQ ID NO:11 comprises an initiating methionine

residue at nucleotides 2-4 and a "TAA" stop codon from nucleotides 713-715. The open reading frame of SEQ ID NO:3 provides for a 237 amino acid HIV-1 Nef protein which comprises a tPA leader sequence fused to amino acids 6-216 of HIV-1 Nef, including the dileucine motif at amino acid residues 174 and 175. This 237 amino acid tPA/Nef (jfrl) fusion protein is disclosed herein as SEQ ID NO:12, and is shown as follows:

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly  
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ser Lys Arg Ser Val Pro  
 Gly Trp Ser Thr Val Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala  
 10 Asp Arg Val Arg Arg Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val  
 Ser Arg Asp Leu Glu Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala  
 Ala Thr Asn Ala Asp Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu  
 Val Gly Phe Pro Val Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr  
 Lys Gly Ala Val Asp Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu  
 15 Glu Gly Leu Ile His Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp  
 Val Tyr His Thr Gln Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro  
 Gly Pro Gly Ile Arg Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu  
 Val Pro Val Glu Pro Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn  
 Asn Cys Leu Leu His Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu  
 20 Lys Glu Val Leu Glu Trp Arg Phe Asp Ser Lys Leu Ala Phe His His  
 Val Ala Arg Glu Leu His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:12).

Therefore, this exemplified Nef protein, Opt tPA-Nef, contains both a tPA leader sequence as well as deleting the myristylation site of Gly-2A DNA molecule encoding HIV-1 Nef from the HIV-1 jfrl isolate wherein the codons are optimized for expression in a mammalian system such as a human.

In another specific embodiment of the present invention, a DNA molecule is disclosed which encodes optimized HIV-1 Nef wherein the open reading frame of a recombinant adenoviral HIV vaccine encodes for modifications at the amino terminal myristylation site (Gly-2 to Ala-2) and substitution of the Leu-174-Leu-175 dileucine motif to Ala-174-Ala-175. This open reading frame is herein described as opt nef (G2A,LLAA) and is disclosed as SEQ ID NO:13, which comprises an initiating methionine residue at nucleotides 12-14 and a "TAA" stop codon from nucleotides 660-662. The nucleotide sequence of this codon optimized version of HIV-1 jfrl nef gene with the above mentioned modifications is disclosed herein as SEQ ID NO:13, as follows:

GATCTGCCAC CATGGCCGGC AAGTGGTCCA AGAGGTCCGT GCCCGGCTGG TCCACCGTGA  
 GGGAGAGGAT GAGGAGGGCC GAGCCCGCCG CCGACAGGGT GAGGAGGACC GAGCCCGCCG  
 CCGTGGGCGT GGGCGCCGTG TCCAGGGACC TGGAGAAGCA CGGCGCCATC ACCTCCTCCA  
 ACACCGCCGC CACCAACGCC GACTGCGCCT GGCTGGAGGC CCAGGAGGAC GAGGAGGTGG  
 5 GCTTCCCCGT GAGGCCCCAG GTGCCCCCTGA GGCCCATGAC CTACAAGGGC GCCGTGGACC  
 TGTCCCACTT CCTGAAGGAG AAGGGCGGCC TGGAGGGCCT GATCCACTCC CAGAAGAGGC  
 AGGACATCCT GGACCTGTGG GTGTACCACA CCCAGGGCTA CTTCCCCGAC TGGCAGAACT  
 ACACCCCCGG CCCCGGCATC AGGTTCCCCC TGACCTTCGG CTGGTGCTTC AAGCTGGTGC  
 CCGTGGAGCC CGAGAAGGTG GAGGAGGCCA ACGAGGGCGA GAACAACGTC GCCGCCACC  
 10 CCATGTCCA GCACGGCATC GAGGACCCCG AGAAGGAGGT GCTGGAGTGG AGGTTGACT  
 CCAAGCTGGC CTTCCACCAC GTGGCCAGGG AGCTGCACCC CGAGTACTAC AAGGACTGCT  
 AAAGCCCGGG C (SEQ ID NO:13).

The open reading frame of SEQ ID NO:13 encodes Nef (G2A,LLAA), disclosed herein as SEQ ID NO:14, as follows:

15 Met Ala Gly Lys Trp Ser Lys Arg Ser Val Pro Gly Trp Ser Thr Val  
 Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala Asp Arg Val Arg Arg  
 Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val Ser Arg Asp Leu Glu  
 Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala Ala Thr Asn Ala Asp  
 Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu Val Gly Phe Pro Val  
 20 Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr Lys Gly Ala Val Asp  
 Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu Glu Gly Leu Ile His  
 Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp Val Tyr His Thr Gln  
 Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro Gly Pro Gly Ile Arg  
 Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu Val Pro Val Glu Pro  
 25 Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn Asn Cys Ala Ala His  
 Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu Lys Glu Val Leu Glu  
 Trp Arg Phe Asp Ser Lys Leu Ala Phe His His Val Ala Arg Glu Leu  
 His Pro Glu Tyr Tyr Lys Asp Cys Ser (SEQ ID NO:14).

30 An additional embodiment of the present invention relates to another DNA  
 molecule encoding optimized HIV-1 Nef wherein the amino terminal myristylation  
 site and dileucine motif have been deleted, as well as comprising a tPA leader peptide.  
 This DNA molecule, opt tpanef (LLAA) comprises an open reading frame which  
 encodes a Nef protein containing a tPA leader sequence fused to amino acid residue  
 6-216 of HIV-1 Nef (jfr1), wherein Leu-174 and Leu-175 are substituted with Ala-174  
 35 and Ala-175 (Ala-195 and Ala-196 in this tPA-based fusion protein). The nucleotide

sequence comprising the open reading frame of opt tpanef (LLAA) is disclosed herein as SEQ ID NO:15, as shown below:

CATGGATGCA ATGAAGAGAG GGCTCTGCTG TGTGCTGCTG CTGTGTGGAG CAGTCTTCGT  
 TTCGCCCAGC GAGATCTCCT CCAAGAGGTC CGTGCCCGGC TGGTCCACCG TGAGGGAGAG  
 5 GATGAGGAGG GCCGAGCCCG CCGCCGACAG GGTGAGGAGG ACCGAGCCCG CCGCCGTGGG  
 CGTGGGCGCC GTGTCCAGGG ACCTGGAGAA GCACGGCGCC ATCACCTCCT CCAACACCGC  
 CGCCACCAAC GCCGACTGCG CCTGGCTGGA GGCCAGGAG GACGAGGAGG TGGGCTTCCC  
 CGTGAGGCCC CAGGTGCCCC TGAGGCCCAT GACCTACAAG GGCGCCGTGG ACCTGTCCCA  
 CTTCTGAAG GAGAAGGGCG GCCTGGAGGG CCTGATCCAC TCCCAGAAGA GGCAGGACAT  
 10 CCTGGACCTG TGGGTGTACC ACACCCAGGG CTACTTCCCC GACTGGCAGA ACTACACCCC  
 CGGCCCCGGC ATCAGGTTCC CCCTGACCTT CGGCTGGTGC TTCAAGCTGG TGGCCGTGGA  
 GCCCGAGAAG GTGGAGGAGG CCAACGAGGG CGAGAACAAC TGCGCCGCC ACCCCATGTC  
 CCAGCACGGC ATCGAGGACC CCGAGAAGGA GGTGCTGGAG TGGAGGTTCG ACTCCAAGCT  
 GGCCTTCCAC CACGTGGCCA GGGAGCTGCA CCCCAGTAC TACAAGGACT GCTAAAGCCC  
 15 (SEQ ID NO:15).

The open reading frame of SEQ ID NO:7 encoding tPA-Nef (LLAA), disclosed herein as SEQ ID NO:16, is as follows:

Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly  
 Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ser Lys Arg Ser Val Pro  
 20 Gly Trp Ser Thr Val Arg Glu Arg Met Arg Arg Ala Glu Pro Ala Ala  
 Asp Arg Val Arg Arg Thr Glu Pro Ala Ala Val Gly Val Gly Ala Val  
 Ser Arg Asp Leu Glu Lys His Gly Ala Ile Thr Ser Ser Asn Thr Ala  
 Ala Thr Asn Ala Asp Cys Ala Trp Leu Glu Ala Gln Glu Asp Glu Glu  
 Val Gly Phe Pro Val Arg Pro Gln Val Pro Leu Arg Pro Met Thr Tyr  
 25 Lys Gly Ala Val Asp Leu Ser His Phe Leu Lys Glu Lys Gly Gly Leu  
 Glu Gly Leu Ile His Ser Gln Lys Arg Gln Asp Ile Leu Asp Leu Trp  
 Val Tyr His Thr Gln Gly Tyr Phe Pro Asp Trp Gln Asn Tyr Thr Pro  
 Gly Pro Gly Ile Arg Phe Pro Leu Thr Phe Gly Trp Cys Phe Lys Leu  
 Val Pro Val Glu Pro Glu Lys Val Glu Glu Ala Asn Glu Gly Glu Asn  
 30 Asn Cys Ala Ala His Pro Met Ser Gln His Gly Ile Glu Asp Pro Glu  
 Lys Glu Val Leu Glu Trp Arg Phe Asp Ser Lys Leu Ala Phe His His  
 Val Ala Arg Glu Leu His Pro Glu Tyr Tyr Lys Asp Cys (SEQ ID NO:16).

An adenoviral vector of the present invention may comprise a DNA sequence,  
 regardless of codon usage, which expresses a wild type or modified Nef protein as  
 35 described herein, including but not limited to modified Nef proteins which comprise a  
 deletion or substitution of Gly 2, a deletion or substitution of Leu 174 and Leu 175

and/or inclusion of a leader sequence. Therefore, partial or fully codon optimized DNA vaccine expression vector constructs are preferred since such constructs should result in increased host expression. However, it is within the scope of the present invention to utilize "non-codon optimized" versions of the constructs disclosed herein,  
 5 especially modified versions of HIV Nef which are shown to promote a substantial cellular immune response subsequent to host administration.

Figure 20A-C show nucleotide sequences at junctions between nef coding sequence and plasmid backbone of nef expression vectors V1Jns/nef (Figure 20A), V1Jns/nef(G2A,LLAA) (Figure 20B), V1Jns/tpanef (Figure 20C) and  
 10 V1Jns/tpanef(LLAA) (Figure 20C, also). 5' and 3' flanking sequences of codon optimized nef or codon optimized nef mutant genes are indicated by bold/italic letters; nef and nef mutant coding sequences are indicated by plain letters. Also indicated (as underlined) are the restriction endonuclease sites involved in construction of respective nef expression vectors. V1Jns/tpanef and V1Jns/tpanef(LLAA) have  
 15 identical sequences at the junctions.

Figure 21 shows a schematic presentation of nef and nef derivatives. Amino acid residues involved in Nef derivatives are presented. Glycine 2 and Leucine 174 and 175 are the sites involved in myristylation and dileucine motif, respectively.

## 20 EXAMPLE 19

### MRKAd5Pol Construction and Virus Rescue

*Construction of vector: shuttle plasmid and pre-adenovirus plasmid* - Key steps performed in the construction of the vectors, including the pre-adenovirus plasmid denoted MRKAd5pol, is depicted in Figure 22. Briefly, the adenoviral shuttle  
 25 vector for the full-length inactivated HIV-1 pol gene is as follows. The vector MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHPA(str.) is a derivative of the shuttle vector used in the construction of the MRKAd5gag adenoviral pre-plasmid. The vector contains an expression cassette with the hCMV promoter (no intronA) and the bovine growth hormone polyadenylation signal. The expression unit has been  
 30 inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*II site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1-/E3+)ClaI (or MRKpAdHVE3) pre-plasmid. The vector, similar to the original shuttle vector contains the *Pac*I site, extension to the packaging signal region, and extension to the pIX gene. The synthetic  
 35 full-length codon-optimized HIV-1 pol gene was isolated directly from the plasmid pV1Jns-HIV-pol-inact(opt). Digestion of this plasmid with *Bgl* II releases the pol

gene intact (comprising a codon optimized IA pol sequence as disclosed in SEQ ID NO:3). The pol fragment was gel purified and ligated into the MRKpdelE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) shuttle vector at the *Bgl*III site. The clones were checked for the correct orientation of the gene by using  
 5 restriction enzymes *Dra*III/*Not*I. A positive clone was isolated and named MRKpdel+hCMVmin+FL-pol+bGHpA(s). The genetic structure of this plasmid was verified by PCR, restriction enzyme and DNA sequencing. The pre-adenovirus plasmid was constructed as follows. Shuttle plasmid MRKpdel+hCMVmin+FL-pol+bGHpA(S) was digested with restriction enzymes *Pac*I and *Bst*1107 I (or its isoschizomer, *Bst*Z107 I) and then co-transformed into *E. coli* strain BJ5183 with  
 10 linearized (*Cla*I digested) adenoviral backbone plasmid, MRKpAd(E1-/E3+)ClaI. The resulting pre-plasmid originally named MRKpAd+hCMVmin+FL-pol+bGHpA(S)E3+ is now referred to as "pMRKAd5pol". The genetic structure of the resulting pMRKAd5pol was verified by PCR, restriction enzyme and DNA  
 15 sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for preparative production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the pol transgene in transient transfection cell culture. The complete nucleotide sequence of this pMRKAd5HIV-1pol adenoviral vector is shown in Figure 26 A-AO.

20 *Generation of research-grade recombinant adenovirus* - The pre-adenovirus plasmid, pMRKAd5pol, was rescued as infectious virions in PER.C6<sup>®</sup> adherent monolayer cell culture. To rescue infectious virus, 12 µg of pMRKAd5pol was digested with restriction enzyme *Pac*I (New England Biolabs) and 3.3 µg was transfected per 6 cm dish of PER.C6<sup>®</sup> cells using the calcium phosphate co-  
 25 precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech Inc.). *Pac*I digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6<sup>®</sup> cells. Infected cells and media were harvested 6 -10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. Infected cells and media were stored at ≤ -60°C. This pol containing  
 30 recombinant adenovirus is referred to herein as "MRKAd5pol". This recombinant adenovirus expresses an inactivated HIV-1 Pol protein as shown in SEQ ID NO:6.

## EXAMPLE 20

### MRKAd5Nef Construction and Virus Rescue

35 *Construction of vector: shuttle plasmid and pre-adenovirus plasmid* - Key steps performed in the construction of the vectors, including the pre-adenovirus

plasmid denoted MRKAd5nef, is depicted in Figure 23. Briefly, as shown in Example 19 above, the vector

MRKpdeIE1(Pac/pIX/pack450)+CMVmin+BGHpA(str.) is the shuttle vector used in the construction of the MRKAd5gag adenoviral pre-plasmid. It has been modified to contain the *Pac*1 site, extension to the packaging signal region, and extension to the pIX gene. It contains an expression cassette with the hCMV promoter (no intronA) and the bovine growth hormone polyadenylation signal. The expression unit has been inserted into the shuttle vector such that insertion of the gene of choice at a unique *Bgl*II site will ensure the direction of transcription of the transgene will be Ad5 E1 parallel when inserted into the MRKpAd5(E1-/E3+)Cla1 pre-plasmid. The synthetic full-length codon-optimized HIV-1 nef gene was isolated directly from the plasmid pV1Jns/nef (G2A,LLAA). Digestion of this plasmid with *Bgl*II releases the pol gene intact, which comprises the nucleotide sequence as disclosed in SEQ ID NO:13. The nef fragment was gel purified and ligated into the

MRKpdeIE1+CMVmin+BGHpA(str.) shuttle vector at the *Bgl*II site. The clones were checked for correction orientation of the gene by using restriction enzyme *Sca*I. A positive clone was isolated and named MRKpdeIE1hCMVminFL-nefBGHpA(s). The genetic structure of this plasmid was verified by PCR, restriction enzyme and DNA sequencing. The pre-adenovirus plasmid was constructed as follows. Shuttle plasmid MRKpdeIE1hCMVminFL-nefBGHpA(s) was digested with restriction enzymes *Pac*1 and *Bst*1107 I (or its isoschizomer, *Bst*Z107 I) and then co-transformed into *E. coli* strain BJ5183 with linearized (*Cla*1 digested) adenoviral backbone plasmid, MRKpAd(E1/E3+)Cla1. The resulting pre-plasmid originally named MRKpdeIE1hCMVminFL-nefBGHpA(s) is now referred to as "pMRKAd5nef". The genetic structure of the resulting pMRKAd5nef was verified by PCR, restriction enzyme and DNA sequence analysis. The vectors were transformed into competent *E. coli* XL-1 Blue for preparative production. The recovered plasmid was verified by restriction enzyme digestion and DNA sequence analysis, and by expression of the nef transgene in transient transfection cell culture. The complete nucleotide sequence of this pMRKAd5HIV-1nef adenoviral vector is shown in Figure 27A-AM.

*Generation of research-grade recombinant adenovirus* - The pre-adenovirus plasmid, pMRKAd5nef, was rescued as infectious virions in PER.C6<sup>®</sup> adherent monolayer cell culture. To rescue infectious virus, 12 µg of pMRKAdnef was digested with restriction enzyme *Pac*1 (New England Biolabs) and 3.3 µg was transfected per 6 cm dish of PER.C6<sup>®</sup> cells using the calcium phosphate co-precipitation technique (Cell Pfect Transfection Kit, Amersham Pharmacia Biotech

Inc.). *Pac1* digestion releases the viral genome from plasmid sequences allowing viral replication to occur after entry into PER.C6<sup>®</sup> cells. Infected cells and media were harvested 6-10 days post-transfection, after complete viral cytopathic effect (CPE) was observed. Infected cells and media were stored at  $\leq -60^{\circ}\text{C}$ . This nef containing recombinant adenovirus is now referred to as "MRKAd5nef".

### EXAMPLE 21

#### Construction of Murine CMV Promoter Containing Shuttle Vectors for Inactivated Pol and Nef/G2A,LLAA

The murine CMV (mCMV) was amplified from the plasmid pMH4 (supplied by Frank Graham, McMaster University) using the primer set: mCMV (*Not* I) Forward: 5'-ATA AGA ATG CGG CCG CCA TAT ACT GAG TCA TTA GG-3' (SEQ ID NO: 20); mCMV (*Bgl* II) Reverse: 5'-AAG GAA GAT CTA CCG ACG CTG GTC GCG CCT C-3' (SEQ ID NO:21). The underlined nucleotides represent the *Not* I and the *Bgl* II sites respectively for each primer. This PCR amplicon was used for the construction of the mCMV shuttle vector containing the transgene in the E1 parallel orientation. The hCMV promoter was removed from the original shuttle vector (containing the hCMV-gag-bGHpA transgene in the E1 parallel orientation) by digestion with *Not* I and *Bgl* II. The mCMV promoter (*Not* I/*Bgl* II digested PCR product) was inserted into the shuttle vector in a directional manner. The shuttle vector was then digested with *Bgl* II and the gag reporter gene (*Bgl* II fragment) was re-inserted back into the shuttle vector. Several clones were screened for correct orientation of the reporter gene. For the construction of the mCMV-gag in the E1 antiparallel orientation, the mCMV promoter was amplified from the plasmid pMH4 using the following primer set: mCMV (*Asc* I) Forward: 5'- ATA AGA ATG GCG CGC CAT ATA CTG AGT CAT TAG G (SEQ ID NO:22); mCMV (*Bgl* II) Reverse: 5' AAG GAA GAT CTA CCG ACG CTG GTC GCG CCT C (SEQ ID NO:23). The underlined nucleotides represent the *Asc* I and *Bgl* II sites, respectively for each primer. The shuttle vector containing the hCMV-gag transgene in the E1 antiparallel orientation was digested with *Asc* I and *Bgl* II to remove the hCMV-gag portion of the transgene. The mCMV promoter (*Asc* I/*Bgl* II digested PCR product) was inserted into the shuttle vector in a directional manner. The vector was then digested with *Bgl* II and the gag reporter gene (*Bgl* II fragment) was re-inserted. Several clones were screened for correct orientation of the reporter gene. For each of the full length IA pol and full length nef/G2A,LLAA genes, cloning was performed using the unique

*Bgl* II site within the mCMV-bGHpA shuttle vector. The pol and nef genes were excised from their respective pV1Jns plasmids by *Bgl* II digestion.

#### EXAMPLE 22

##### 5 Construction of mCMV Full Length Inactivated Pol and Full Length nef/G2A.LLAA Adenovectors

Each of these transgenes of Example 21 were inserted into the modified shuttle vector in both the E1 parallel and E1 anti-parallel orientations. *Pac* I and *Bst* Z110I digestion of each shuttle vector was performed and each specific transgene  
10 fragment containing the flanking Ad5 sequences was isolated and co-transformed with *Cla* I digested MRKpAd5(E3+) or MRKpAd5(E3-) adenovector plasmids via bacterial homologous recombination in BJ5183 *E. coli* cells. Recombinant pre-plasmid adenovectors containing the various transgenes in both the E3- and E3+ versions (and in the E1 parallel and E1 antiparallel orientations) were subsequently  
15 prepared in large scale following transformation into XL-1 Blue *E. coli* cells and analyzed by restriction analysis and sequencing.

#### EXAMPLE 23

##### Construction of hCMV-tpa-nef (LLAA) Adenovector

20 The tpa-nef gene was amplified out from GMP grade pV1Jns-tpanef (LLAA) vector using the primer sets: Tpanef (BamHI) F 5'-ATT GGA TCC ATG GAT GCA ATG AAG AGA GGG (SEQ ID 24); Tpanef (BamHI) R 5'-ATA GGA TCC TTA GCA GTC CTT GTA GTA CTC G (SEQ ID NO:25). The resulting PCR product was digested with *Bam*HI, gel purified and cloned into the *Bgl* II site of MRKAd5CMV-bGHpA shuttle vector (*Bgl* II digested and calf intestinal phosphatase treated).  
25 Clones containing the tpanef (LLAA) gene (see SEQ ID NO:15 for complet coding region) in the correct orientation with respect to the hCMV promoter were selected following *Sca* I digestion. The resulting MRKAd5tpanef shuttle vector was digested with *Pac* I and *Bst* Z1101 and cloned into the E3+ MRKAd5 adenovector via bacterial  
30 homologous recombination techniques.

#### EXAMPLE 24

##### Immunogenicity of MRKAd5pol and MRKAd5nef Vaccine

Materials and Methods - Rodent Immunization - Groups of N=10 BALB/c  
35 mice were immunized i.m. with the following vectors: (1) MRKAd5hCMV-IApol (E3+) at either  $10^7$  vp and  $10^9$  vp; and (2) MRKAd5hCMV-IApol (E3-) at either

10<sup>7</sup> vp and 10<sup>9</sup> vp. At 7 weeks post dose, 5 of the 10 mice per cohort were boosted with the same vector and dose they initially received. At 3 weeks post the second dose, sera and spleens were collected from all the animals for RT ELISA and IFN $\gamma$  ELISPOT analyses, respectively. For all rodent immunizations, the Ad5 vectors were  
5 diluted in 5 mM Tris, 5% sucrose, 75 mM NaCl, 1 mM MgCl<sub>2</sub>, 0.005% polysorbate 80, pH 8.0. The total dose was injected to both quadriceps muscles in 50  $\mu$ L aliquots using a 0.3-mL insulin syringe with 28-1/2G needles (Becton-Dickinson, Franklin Lakes, NJ).

Groups of N=10 C57/BL6 mice were immunized i.m. with the following  
10 vectors: (1) MRKAd5hCMV-nef(G2A,LLAA) (E3+) at either 10<sup>7</sup> vp and 10<sup>9</sup> vp; (2) MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10<sup>7</sup> vp and 10<sup>9</sup> vp; and (3) MRKAd5mCMV-tpanef(LLAA) (E3+) at either 10<sup>7</sup> vp and 10<sup>9</sup> vp. At 7 weeks post dose, 5 of the 10 mice per cohort were boosted with the same vector and dose they initially received. At 3 weeks post the second dose, sera and spleens were  
15 collected from all the animals for RT ELISA and IFN $\gamma$  ELISPOT analyses, respectively.

*Non-human Primate immunization* - Cohorts of 3 rhesus macaques (2-3 kg) were vaccinated with the following Ad vectors: (1) MRKAd5hCMV-IAPol (E3+) at either 10<sup>9</sup> vp and 10<sup>11</sup> vp dose; and (2) MRKAd5hCMV-IAPol (E3-) at either  
20 10<sup>9</sup> vp and 10<sup>11</sup> vp; (3) MRKAd5hCMV-nef(G2A,LLAA) (E3+) at either 10<sup>9</sup> vp and 10<sup>11</sup> vp; and (4) MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10<sup>9</sup> vp and 10<sup>11</sup> vp. The vaccine was administered to chemically restrained monkeys (10 mg/kg ketamine) by needle injection of two 0.5 mL aliquots of the Ad vectors (in 5 mM Tris, 5% sucrose, 75 mM NaCl, 1 mM MgCl<sub>2</sub>, 0.005% polysorbate 80, pH 8.0)  
25 into both deltoid muscles. The animals were immunized twice at a 4 week interval (T=0, 4 weeks).

*Murine anti-RT and anti-nef ELISA* - Anti-RT titers were obtained following standard secondary antibody-based ELISA. Maxisorp plates (NUNC, Rochester, NY) were coated by overnight incubation with 100  $\mu$ L of 1  $\mu$ g/mL HIV-1 RT protein  
30 (Advanced Biotechnologies, Columbia, MD) in PBS. For anti-nef ELISA, 100  $\mu$ L of 1  $\mu$ g/mL HIV-1 nef (Advanced Biotechnologies, Columbia, MD) was used to coat the plates. The plates were washed with PBS/0.05% Tween 20 using Titertek MAP instrument (Huntsville, AL) and incubated for 2 h with 200  $\mu$ L/well of blocking solution (PBS/0.05% tween/1% BSA). An initial serum dilution of 100-fold was  
35 performed followed by 4-fold serial dilution. 100- $\mu$ L aliquots of serially diluted samples were added per well and incubated for 2 h at room temperature. The plates

were washed and 100  $\mu$ L of 1/1000-diluted HRP-rabbit anti-mouse IgG (ZYMED, San Francisco, CA) were added with 1 h incubation. The plates were washed thoroughly and soaked with 100  $\mu$ L 1,2-phenylenediamine dihydrochloride/hydrogen peroxide (DAKO, Norway) solution for 15 min. The reaction was quenched by adding 100  $\mu$ L of 0.5M H<sub>2</sub>SO<sub>4</sub> per well. OD<sub>492</sub> readings were recorded using Titertek Multiskan MCC/340 with S20 stacker. Endpoint titers were defined as the highest serum dilution that resulted in an absorbance value of greater than or equal to 0.1 OD<sub>492</sub> (2.5 times the background value).

*Non-human primate and murine ELISpot assays* - The enzyme-linked immuno-spot (ELISpot) assay was utilized to enumerate antigen-specific INF $\gamma$ -secreting cells from mouse spleens (Miyahira, et al.1995, *J. Immunol. Methods* 181:45-54) or macaque PBMCs. Mouse spleens were pooled from 5 mice/cohort and single cell suspensions were prepared at  $5 \times 10^6$ /mL in complete RPMI media (RPMI1640, 10% FBS, 2mM L-glutamine, 100U/mL Penicillin, 100 u/mL streptomycin, 10 mM Hepes, 50 uM  $\beta$ -ME). Rhesus PBMCs were prepared from 8-15 mL of heparinized blood following standard Ficoll gradient separation (Coligan, et al, 1998, *Current Protocols in Immunology*. John Wiley & Sons, Inc.). Multiscreen opaque plates (Millipore, France) were coated with 100  $\mu$ L/well of either 5  $\mu$ g/mL purified rat anti-mouse IFN- $\gamma$  IgG1, clone R4-6A2 (Pharmingen, San Diego, CA), or 15 ug/mL mouse anti-human IFN- $\gamma$  IgG<sub>2a</sub> (Cat. No. 1598-00, R&D Systems, Minneapolis, MN) in PBS at 4°C overnight for murine or monkey assays, respectively. The plates were washed with PBS/penicillin/streptomycin and blocked with 200  $\mu$ L/well of complete RPMI media for 37 °C for at least 2 h.

To each well, 50  $\mu$ L of cell samples ( $4-5 \times 10^5$  cells per well) and 50  $\mu$ L of the antigen solution were added. To the control well, 50  $\mu$ L of the media containing DMSO were added; for specific responses, either selected peptides or peptide pools (4 ug/mL per peptide final concentration) were added. For BALB/c mice immunized with the pol constructs, stimulation was conducted using a pool of CD4<sup>+</sup>-epitope containing 20-mer peptides (aa21-40, aa411-430, aa641-660, aa731-750, aa771-790) or a pool of CD8<sup>+</sup>-epitope containing peptides (aa201-220, aa311-330, aa781-800). For C57/BL6 mice immunized with the nef construct, either aa51-70 (CD8<sup>+</sup> T cell epitope) or aa81-100 (CD4<sup>+</sup>) peptide derived from the nef sequence was added for specific stimulation. In monkeys, the responses against pol were evaluated using two pools (L and R) of 20-aa peptides that encompass the entire pol sequence and overlap by 10 amino acids. In monkeys vaccinated with the nef constructs, a single pool containing 20-mer peptides covering the entire HIV-1 nef sequence and overlapping

by 10 aa was used. Each sample/antigen mixture was performed in triplicate wells for murine samples or in duplicate wells for rhesus PBMCs. Plates were incubated at 37°C, 5% CO<sub>2</sub>, 90% humidity for 20-24 h. The plates were washed with PBS/0.05% Tween 20 and incubated with 100 µL/well of either 1.25 µg/mL biotin-conjugated rat anti-mouse IFN-γ mAb, clone XMG1.2 (Pharmingen) or of 0.1 µg/mL biotinylated anti-human IFN-γ goat polyclonal antibody (R&D Systems) at 4°C overnight. The plates were washed and incubated with 100 µL/well 1/2500 dilution of streptavidin-alkaline phosphatase conjugate (Pharmingen) in PBS/0.005% Tween/5% FBS for 30 min at 37 °C. Spots were developed by incubating with 100 µL/well 1-step NBT/BCIP (Pierce Chemicals) for 6-10 min. The plates were washed with water and allowed to air dry. The number of spots in each well was determined using a dissecting microscope and the data normalized to 10<sup>6</sup> cell input.

*Non-human Primate anti-RT ELISA* - The pol-specific antibodies in the monkeys were measured in a competitive RT EIA assay, wherein sample activity is determined by the ability to block RT antigen from binding to coating antibody on the plate well. Briefly, Maxisorp plates were coated with saturating amounts of pol positive human serum (#97111234). 250 µL of each sample is incubated with 15 µL of 266 ng/mL RT recombinant protein (in RCM 563, 1% BSA, 0.1% tween, 0.1% NaN<sub>3</sub>) and 20 µL of lysis buffer (Coulter p24 antigen assay kit) for 15 min at room temperature. Similar mixtures are prepared using serially diluted samples of a standard and a negative control which defines maximum RT binding. 200 µL/well of each sample and standard were added to the washed plate and the plate incubated 16-24 h at room temperature. Bound RT is quantified following the procedures described in Coulter p24 assay kit and reported in milliMerck units per mL arbitrarily defined by the chosen standard.

*Results - Rodent Studies* - BALB/c mice (n=5 mice/cohort) were immunized once or twice with varying doses of MRKAd5hCMV-IApol(E3+) and MRKAd5hCMV-IApol(E3-). At 3 weeks after the second dose, Anti-pol IgG levels were determined by an ELISA assay using RT as a surrogate antigen. Cellular response were quantified via IFNγ ELISpot assay against pools of pol-epitope containing peptides. The results of these assays are summarized in Table 10. The results indicate that the mouse vaccinees exhibited detectable anti-RT IgGs with an adenovector dose as low as 10<sup>7</sup> vp. The humoral responses are highly dose-dependent and are boostable with a second immunization. One or two doses of either pol vectors elicit high frequencies of antigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells; the responses are weakly dose-dependent but are boostable with a second immunization.

Table 10. Immunogenicity of MRKAd5pol Vectors in BALB/c mice.

Group	Vaccine	Dose	No. of Doses	Anti-RT IgG Titers <sup>a</sup>			SFC/10 <sup>6</sup> cells <sup>b</sup>		
				GMT	+SE	-SE	Medium	CD4+ peptide pool	CD8+ peptide pool
1	MRKAd5hCMVFLpol (E3+)	10 <sup>7</sup> vp	2 1	310419 919	301785 372	153020 265	1(1) 1(1)	75(4) 72(9)	2313(67) 533(41)
2	MRKAd5hCMVFLpol (E3+)	10 <sup>9</sup> vp	2 1	1638400 <sup>b</sup> 713155	0 528520	0 303555	2(2) 1(1)	114(9) 48(7)	2063(182) 733(89)
3	MRKAd5hCMVFLpol (E3-)	10 <sup>7</sup> vp	2 1	310419 6400	386218 14013	172097 4393	0(0) 10(8)	223(7) 141(21)	2807(27) 409(28)
4	MRKAd5hCMVFLpol (E3-)	10 <sup>9</sup> vp	2 1	1638400 <sup>b</sup> 1241675 <sup>b</sup>	0 396725	0 300661	1(1) 0(0)	180(13) 39(13)	2385(11) 833(83)
5	Naïve	none	none	57	9	7	9(2)	11(4)	10(1)

<sup>a</sup>GMT, geometric mean titer of the cohort of 5 mice; SE, standard error of the geometric mean<sup>b</sup>Near or at the upper limit of the serial dilution; hence, could be greater than this value<sup>c</sup>No. of Spot-forming Cells per million splenocytes; mean values of triplicates are reported along with standard errors in parenthesis.

- 5 C57/BL6 mice were immunized once or twice with varying doses of MRKAd5hCMV-nef(G2A,LLAA) (E3+), MRKAd5mCMV-nef(G2A,LLAA) (E3+) at either 10<sup>7</sup> vp and (3) MRKAd5mCMV-tpanef(LLAA) (E3+) at either 10<sup>7</sup> vp and 10<sup>9</sup> vp. The immune response were analyzed using similar protocols and the results are listed in Table 11. While anti-nef IgG responses could not be detected in this
- 10 model system with any of the constructs, there are strong indications of a cellular immunity generated against nef using the ELISpot assay.

Table 11. Immunogenicity of MRKAd5nef Vectors in C57/BL6 mice.

Group	Vaccine	Dose	No. of Doses	Anti-nef IgG Titers <sup>a</sup>			SFC/10 <sup>6</sup> cells <sup>b</sup>		
				GMT	+SE	-SE	Medium	aa51-70 CD8+	aa81-100 CD4+
1	MRKAd5hCMVFLnef (E3+)	10 <sup>7</sup> vp	2 1	174 132	70 42	50 32	1(1) 0(0)	23(1) 0(0)	1(1) 0(0)
2	MRKAd5hCMVFLnef (E3+)	10 <sup>9</sup> vp	2 1	174 132	70 42	50 32	0(0) 1(1)	61(7) 62(7)	4(2) 3(1)
3	MRKAd5mCMVFLnef (E3+)	10 <sup>7</sup> vp	2 1	132 115	42 46	32 33	3(1) 3(2)	15(5) 3(2)	5(2) 4(2)
4	MRKAd5mCMVFLnef (E3+)	10 <sup>9</sup> vp	2 1	132 132	42 42	32 32	4(2) 2(1)	83(13) 29(2)	5(1) 4(0)
5	MRKAd5mCMVtpanef(E3+)	10 <sup>7</sup> vp	2 1	132 100	42 0	32 0	3(2) 3(1)	14(2) 13(4)	5(1) 10(3)
6	MRKAd5mCMVtpanef(E3+)	10 <sup>9</sup> vp	2 1	230 115	170 46	98 33	3(2) 7(1)	145(29) 151(14)	4(0) 10(0)
7	Naïve	none	none	152	78	52	21(2)	18(8)	26(3)

<sup>a</sup>GMT, geometric mean titer of the cohort of 5 mice; SE, standard error of the geometric mean<sup>b</sup>No. of spot-forming cells per million splenocytes; mean values of triplicates are reported along with standard errors in parenthesis.

15

*Monkey Studies* - Cohorts of 3 rhesus macaques were immunized with 2 doses of MRKAd5hCMV-IApol(E3+) and MRKAd5hCMV-IApol(E3-). The number of antigen-specific T cells (per million PBMCs) were enumerated using one of two

- peptide pools (L and R) that cover the entire pol sequence; the results are listed in Table 12. Moderate-to-strong T cell responses were detected in the vaccinees using either constructs even at a low dose of  $10^9$  vp. Longitudinal analyses of the anti-RT antibody titers in the animals suggest that the pol transgene product is expressed efficiently to elicit a humoral response (Table 13). It would appear that generally higher immune responses were observed in animals that received the E3- construct compared to the E3+ virus.

Table 12. Pol-specific T Cell Responses in MRKAd5pol Immunized Rhesus Macaques.

Vaccine (T=0,4 wks)	Monkey #	Prebleed			T=4			T=7			T=16		
		Mock	Pol L	Pol R	Mock	Pol L	Pol R	Mock	Pol L	Pol R	Mock	Pol L	Pol R
MRKAd5hCMV-IAPol(E3+) $10^{11}$ vp	99C100	1	0	0	1	38	31	0	52	146	0	49	715
	99C215	1	2	2	10	98	249	1	109	305	22	88	250
	99D201	5	5	4	6	149	95	0	40	35	0	35	18
MRKAd5hCMV-IAPol(E3+) $10^9$ vp	99D212	0	2	0	4	331	114	0	58	14	0	6	6
	99D180	0	4	2	0	19	192	4	36	156	5	38	108
	99C201	8	5	21	6	62	62	0	18	32	1	14	65
MRKAd5hCMV-IAPol(E3-) $10^{11}$ vp	99D239	5	2	2	20	82	172	1	68	114	9	21	40
	99C186	4	12	6	5	120	421	2	271	489	16	875	530
	99C084	1	8	9	8	84	484	0	14	236	1	24	264
MRKAd5hCMV-IAPol(E3-) $10^9$ vp	CC7C	10	10	8	12	724	745	4	322	376	4	188	176
	CD1G	2	0	1	5	474	468	0	232	212	0	101	121
	CD11	6	6	12	10	98	110	5	60	80	8	25	34
Naïve	083Q	nd	nd	nd	nd	nd	nd	4	2	2	2	1	2

nd, not determined

Reported are SFC per million PBMCs; mean of duplicate wells.

Table 13. Anti-RT Ig Levels in MRKAd5pol Immunized macaques.

RT ANTIBODY ASSAY TITERS IN mMU/mL				
Vaccine/Monkey Tag	T=4	T=7	T=12	T=16
MRKAd5hCMV-IAPol(E3+), $10^{11}$ vp				
99C100	61	1999	5928	4768
99C215	81	1541	2356	2767
99D201	53	336	539	387
MRKAd5hCMV-IAPol(E3+), $10^9$ vp				
99D212	10	40	49	68
99D180	<10	36	79	93
99C201	<10	37	71	76
MRKAd5hCMV-IAPol(E3-), $10^{11}$ vp				
99D239	44	460	1234	1015
99C186	21	233	480	345
99C084	235	2637	2858	1626
MRKAd5hCMV-IAPol(E3-), $10^9$ vp				
CC7C	32	175	306	235
CD1G	20	140	273	419
CD11	15	112	149	237

When rhesus macaques were immunized i.m. with two doses of MRKAd5nef

- 5 constructs, vigorous T cell responses ranging from 100 to as high as 1100 per million were observed in 8 of 12 vaccinees (Table 14). The efficacies of the mCMV- and hCMV- driven nef constructs are comparable on the basis of the data generated thus far.

10 Table 14. Nef-specific T cell Responses in MRKAd5nef Immunized Rhesus Macaques.

Vaccine (T=0,4 wks)	Monk #	Pre		T=4		T=7		T=16	
		Mock	Nef	Mock	Nef	Mock	Nef	Mock	Nef
MRKAd5hCMV-nef(G2A,LLAA) (E3+) 10 <sup>6</sup> 11 vp	CD2D	0	4	31	440	4	368	1	251
	CC7B	0	0	2	521	0	178	1	1522
	CC61	2	9	31	112	0	108	11	100
MRKAd5hCMV-nef(G2A,LLAA) (E3+) 10 <sup>6</sup> 9 vp	CC2K	9	9	6	52	0	35	0	15
	CD15	5	4	30	998	2	586	0	434
	CD16	6	1	6	1146	0	369	1	212
MRKAd5mCMV-nef(G2A,LLAA) (E3+) 10 <sup>6</sup> 11 vp	99D191	1	5	4	614	0	298	2	419
	99D144	4	6	5	434	0	1100	2	932
	99C193	1	2	1	58	1	22	0	64
MRKAd5mCMV-nef(G2A,LLAA) (E3+) 10 <sup>6</sup> 9 vp	99D224	1	11	14	231	1	125	0	70
	99D250	8	9	4	108	0	54	0	5
	99C120	1	6	20	299	0	92	0	79
Naive	083Q	nd	nd	18	22	4	5	2	1

#### EXAMPLE 25

- 15 Comparison of Clade B vs. Clade C T Cell Responses in HIV-Infected Subjects

PBMC samples collected from two dozens of patients infected with HIV-1 in US were tested in ELISPOT assays with peptide pools of 20-mer peptides overlapping by 10 amino acids. Four different peptide pools were tested for cross-clade recognition, and they were either derived from a clade B-based isolate (gag H-b; nef-b) or a clade C-based isolate (gag H-c, nef-c). Data in Table 15 shows that T cells from these patients presumably infected with clade B HIV-1 could recognize clade C gag and nef antigens in ELISPOT assay. Correlation analysis further demonstrated that these T cell responses against clade C gag peptide pool were about 60% of the clade B counterpart (Figure 24), while the T cell responses against clade C nef were about 85% of the clade B counterpart (Figure 25). These results suggest that cellular immune responses generated in patients infected with clade B HIV-1 can recognize gag and nef antigens derived from clade C HIV-1. These data show that a HIV vaccine, such as a DNA or MRKAd5-based adenoviral vaccine expressing a clade B

gag and/or nef antigen will potentially have the ability to provide a prophylactic and/or therapeutic advantage on a global scale.

5

Table 15

Responses Shown as the Number of gIFN-Secreting T Cells per Million PBMCs

subject	bleed date	gag epitope # (from mapping)	mock	gag H-b	gagH-c	nef-b	nef-c
#100	19-Jul-99	12	10	3950	1385	1295	1300
#101	25-Jul-99	3	15	3885	1280	na	1020
#102	25-Jul-99	4	15	1740	850	1255	1785
#104	7-Jun-99	2	5	1355	1185	na	1060
#107	11-Oct-99	2	25	3305	2795	670	870
#405	11-Jul-99	2	15	4575	3180	1700	1500
#501	19-Jul-99	2	15	1100	570	3365	3460
#505	18-Jul-99	5	10	2145	1725	1235	na
#506	28-Feb-99	2	25	150	45	400	610
#701	28-Mar-99	5	30	7620	4775	3320	2780
#709	17-May-99	3	15	2785	1945	1090	1630
#710	24-May-99	4	5	1055	1080	2210	2140

10

## EXAMPLE 26

Characterization and Production of MRKAd5pol and MRKAd5nef  
Vectors in Roller Bottles

*Expansion of nef and pol Adenovectors* - Nef and pol CsCl purified MRKAd5 seeds were used to infect roller bottles to produce P4 virus to be used as a seed for further experiments. P4 MRKAd5 pol and nef vectors were used to infect roller bottles at an MOI 280 vp/cell, except for hCMV-tpa-nef [E3+] which was infected at an MOI of 125 due to low titers of seed obtained at P4.

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Table 16 Viral particle concentrations for P5 nef and pol adenovectors

Adenovector	AEX Titer (10 <sup>10</sup> vp/ml culture)	AEX Titer (10 <sup>4</sup> vp/cell)	Amplification Ratio
hCMV-FL-nef [E3+]	1.1	0.9	30
mCMV-FL-nef [E3+]	2.2	2.1	75
hCMV-tpa-nef [E3+]	0.07	0.1	5
mCMV-tpa-nef [E3+]	1.3	0.9	35
hCMV-FL-pol [E3+]	2.7	2.1	75
hCMV-FL-pol [E3-]	1.9	1.3	45

- 5 *Roller Bottle Passaging* - Passaging of the *pol* and *nef* constructs continued through passage seven. Cell-associated (freeze/thaw lysis) and whole broth (triton-lysis) titers obtained in all passages were very consistent. In general, MRKAd5pol is ca. 70% as productive as MRKAd5gag while MRKAd5nef is ca. 25% as productive as MRKAd5gag. Samples of P7 virus for both constructs were analyzed by V&CB by
- 10 restriction digest analysis and did not show any rearrangements.

Table 17. Passage Six Viral Productivity for MRKAd5pol and MRKAd5nef

		Xviable ( $10^6$ cells/ml), Viability (%)		Cell Passage Number	AEX Titer (Cell Associated) $10^{10}$ vp/ml culture	Titer $10^4$ vp/cell	Amplification Ratio	Triton Lysis Titer $10^{10}$ vp/ml culture
		Infection	Harvest					
hCMV-FL-nef [E3+]	pool	1.22, 85%		62	0.8	0.7	25	1.6
	1		0.99, 62%					
	2		1.10, 72%					
hCMV-FL-pol [E3+]	pool	1.42, 89%		62	4.5	3.2	115	7.0
	1		1.22, 70%					
	2		1.42, 74%					

15 Table 18. Passage Seven Viral Productivity for MRKAd5pol and MRKAd5nef

		Xviable ( $10^6$ cells/ml), Viability (%)		Cell Passage Number	AEX Titer (Cell Associated) $10^{10}$ vp/ml culture	Titer $10^4$ vp/cell	Amplification Ratio	Triton Lysis Titer $10^{10}$ vp/ml culture
		Infection	Harvest					
hCMV-FL-nef [E3+]	Pool	1.33, 90%		66	1.0	0.8	29	2.1
	1		0.96, 70%					
	2		1.18, 73%					
hCMV-FL-pol [E3+]	Pool	0.90*, 90%		56	4.2	4.7	168	6.5
	1		1.18, 88%					
	2		1.04, 80%					

- MRKAd5nef and MRKAd5pol Viral Production Kinetics* - A timecourse experiment was carried out in roller bottles to determine if the viral production kinetics of the MRKAd5pol and MRKAd5nef vectors were similar to those of
- 20 MRKAd5gag. PER.C6<sup>®</sup> cells in roller bottle cultures were infected at an MOI of 280 vp/cells with P5 MRKAd5pol, P5 MRKAd5nef and P7 MRKAd5gag; for each adenovector, two infected bottles were sampled at 24, 36, 48, and 60 hours post infection. In addition, two bottles were left unsampled until 48 hpi when they were harvested under the Phase I process conditions. The anion-exchange HPLC viral
- 25 particle concentrations of the freeze-thaw recovered cell associated virus at the 24, 36,

48, and 60 hpi timepoints are shown in Figure 29A-B. The QPA titers show a similar trend (data not shown).

*Comparison of hCMV- and mCMV-FL-nef* - As the titers obtained with the MRKAd5nef construct (hCMV-FL-nef) were lower than those obtained with MRKAd5gag or MRKAd5pol, a viral productivity comparison experiment was performed with mCMV-FL-nef. For each of the two adenovectors (hCMV- and mCMV-FL-nef), two roller bottles were infected at an MOI of 280 vp/cell with passage five clarified lysate. The macroscopic and microscopic observations of the four roller bottles were identical at the time of harvest. Analysis of the clarified lysate produced indicated a higher viral particle concentration in the bottles infected with mCMV-FL-nef, as shown in Table 19. It is stipulated that the higher productivity with mCMV promoter driven nef vector is due to lower nef expression levels in PER.C6® cells- experiments are underway at V&CB to measure nef expression levels.

Table 19. Passage Six Viral Productivity Comparison of hCMV- and mCMV-FL-nef

		Xv (10 <sup>6</sup> cells/ml), Viability (%)		Cell Passage Number	AEX Titer 10 <sup>10</sup> vp/ml culture	Titer 10 <sup>6</sup> vp/cell	Amplification Ratio	Triton Lysis Titer 10 <sup>10</sup> vp/ml culture
		Infection	Harvest					
hCMV-FL-nef (MRKAd5nef)	Pool	1.11, 91%		60	1.5	1.4	50	2.8
	1		1.23, 75%					
	2		1.34, 74%					
mCMV-FL-nef	Pool	1.11, 91%		60	2.3	2.1	75	4.6
	1		1.49, 84%					
	2		1.18, 77%					

## EXAMPLE 27

### Characterization and Large Scale Production of MRKAd5nef Virus in Bioreactors

*Materials and Methods* - The experiment of the present example was run twice under the following conditions: 36.5°C, DO 30%, pH 7.30, 150rpm agitation rate, no sparging, Life Technologies (Gibco, Invitrogen) 293 SFM II (with 6mM L-glutamine), 0.5M NaOH as base for pH control. During the first run (B20010115), two 10L stirred vessel bioreactors were inoculated with PER.C6® cells at a concentration of 0.2x10<sup>6</sup> cells/ml. Cells were grown until they reached a cell concentration of approximately 1x10<sup>6</sup> cells/ml. The cells were infected with uncloned MRKAd5nef (G2A,LLAA) at a MOI of 280 virus particles (vp)/cell. For the second batch (B20010202), the same procedure as the first run was used, except the cells

were infected with cloned MRAd5nef. During both runs, the bioreactors were harvested 48 hours post-infection. Samples were taken and virus concentrations were determined from whole broth (with triton lysis), supernatant, and cell pellets (3 X freeze/thaw) with the AEX and QPA assays. Metabolites were measured with

5 BioProfile 250 throughout the process.

Table 20: Experimental Conditions

Temperature	36.5 °C
DO	30%
PH	7.30
Agitation	150 rpm
Sparging	None

Table 21: Virus source used for experiments.

10

Run	Batch ID	Cloned/Uncloned MRKAd5nef	MOI (vp/cells)
#1	B20010115-1	Uncloned	280
	B20010115-2	Uncloned	280
#2	B20010202-1	Cloned	280
	B20010202-2	Cloned	280

*Results* - Table 22 and 23 show an the ability to scale up production of MRKAd5nef by growth in a bioreactor.

15

Table 22: Virus Concentration as measured by the AEX assay

Run	Batch ID	Cloned/Uncloned MRKAd5nef	Virus Concentration @ 48hpi (1x10 <sup>13</sup> vp/L)			
			Supernatant	Clarified Lysate	Total	Triton Lysate
#1	B20010115-1	Uncloned	0.72	3.26	3.98	5.76
	B20010115-2	Uncloned	0.38	1.67	2.05	2.46
#2	B20010202-1	Cloned	0.80	6.00	6.80	8.88
	B20010202-2	Cloned	0.50	6.00	6.50	8.47

Table 23: Virus Titers as measured by the QPA assay

Run	Batch ID	Cloned/Uncloned MRKAd5nef	Virus Concentration @ 48hpi (1x10 <sup>11</sup> IU/L)				
			Whole Broth	Supernatant	Clarified Lysate	Total	Triton Lysate
#1	B20010115-1	Uncloned	0.13	1.12	1.76	2.88	11.28
	B20010115-2	Uncloned	0.14	0.73	1.54	2.27	5.86
#2	B20010202-1	Cloned	0.14	0.97	1.62	2.69	11.89
	B20010202-2	Cloned	0.14	1.17	1.70	2.97	12.47

20

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art

from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

#### EXAMPLE 28

##### 5 MRKAd5HIV-1gag Boosting of DNA-Primed Animals

Groups of 3-5 rhesus macaques were immunized with (a) 5 mgs of V1Jns-Flgag (pVIJnsCMV(no intron)-FL-gag-bGHpA), (b) 5 mgs of V1Jns-Flgag formulated with 45 mgs of a non-ionic block copolymer CRL1005, or (c) 5 mgs of  
10 V1Jns-Flgag formulated with 7.5 mgs of CRL1005 and 0.6 mM benzalkonium chloride at weeks 0, 4, and 8. All animals received a single dose of  $10^7$  viral particles (vp) of the MRKAd5HIV-1gag at week 26. Note:  $10^7$  is too low to prime or boost effectively when used as a single modality (dose is selected to mimic preexposure to adenovirus); see Figure 32.

15 Blood samples were collected from all animals at several time points and peripheral blood mononuclear cells (PBMCs) were prepared using standard Ficoll method. The PBMCs were counted and analyzed for gamma-interferon secretion using the ELISpot assay (Table 24). For each monkey, the PBMCs were incubated overnight either in the absence (medium) or presence of a pool (called "gag H") of 50  
20 20-aa long peptides that encompass the entire HIV-1 gag sequence.

The results indicate that MRKAd5HIV-1gag was very effective in boosting the T cell immune responses in these monkeys. At week 28 or 2 weeks after the viral boost, the number of gag-specific T cells per million PBMCs increased 2-48 fold compared to the levels observed at week 24 or 2 weeks prior to the boost.

25 The PBMCs were also analyzed by intracellular gamma-interferon staining prior to (at week 10) and after the MRKAd5gag boost (at week 30). The results for select animals are shown on Figure 31. The results indicate that (a) immunization with DNA/adjuvant formulation elicited T cell responses which can either be balanced,  $CD4^+$ -biased or  $CD8^+$ -biased, and (b) boosting with the MRKAd5gag  
30 construct produced in all cases a strongly  $CD8^+$ -biased response. These results suggest that boosting with MRKAd5HIV-1gag construct is able to improve the levels of antigen-specific  $CD8^+$  T cells.

Table 24. Boosting of DNA/Adjuvant-Primed Rhesus Monkeys with MRKAd5gag

Grp#	Priming T=0, 4, 8 wks DNA/5 mgs PBS (D101)	Boost T=28 wks MRKAd5gag(E3+) 10 <sup>7</sup> vp	Monkey	T=0		T=4		T=6		T=10		T=17		T=24		T=28		T=30	
				Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H	Medium	gag H
1	DNA/5mgs + CRL1005/5mgs	MRKAd5gag(E3+) 10 <sup>7</sup> vp	CB5H	NA	NA	3	35	15	71	4	224	8	115	8	85	19	959	0	316
			CB6X	0	0	0	15	0	46	0	68	0	75	0	35	3	1705	1	755
			AW3G	5	11	0	36	3	51	3	48	2	89	8	65	10	989	0	385
			CC1C	0	4	1	60	0	111	5	270	4	280	8	232	3	959	19	1345
2	DNA/5 mgs + CRL1005/5mgs	MRKAd5gag(E3+) 10 <sup>7</sup> vp	CC1K	4	0	1	101	0	264	0	781	5	452	0	321	0	1915	1	1059
			AW3P	9	8	1	10	4	71	4	154	8	104	5	85	11	838	6	241
			CB5F	NA	NA	0	31	0	288	0	530	19	374	9	251	8	1549	20	1734
			AK8B	9	12	4	35	1	119	0	439	0	425	0	316	4	1229	5	1354
3	DNA/5 mgs + CRL1005/7.5 mgs + 0.6 mM BAK	MRKAd5gag(E3+) 10 <sup>7</sup> vp	AW20	10	4	1	59	5	284	19	425	6	105	8	205	18	565	8	404
			CA4R	1	0	3	121	1	135	1	270	5	130	1	105	14	1384	10	978
			CB5B	8	6	0	6	3	119	0	274	6	282	1	208	0	636	1	828
			CB5W	4	3	0	26	1	91	0	139	0	164	1	62	5	543	1	349
	none	None	CB7D	1	0	0	135	0	318	1	609	5	625	1	759	0	2278	4	1831
4			98D201	3	0	0	0	1	0	0	0	0	1	1	2	3	0	0	0

NA, not available

## EXAMPLE 29

## Construction of gagpol fusion for MRKAd5gagpol fusion constructs

The open reading frames for the codon-optimized HIV-1 gag gene was fused directly to the open reading frame of the IA pol gene (consisting of RT, RNAseH and integrase domains) by stepwise PCR. Because the gene (SEQ ID NO: 38) does not include the protease gene and the frameshift sequence, it encodes a single polypeptide of the combined size of p55, RT, RNAse H and integrase (1350 amino acids; SEQ ID NO: 39).

The fragment that extends from the BstEII site within the gag gene to the last non-stop codon was ligated via PCR to a fragment that extends from the start codon of the IAPol to a unique BamHI site. This fragment was digested with BstEII and BamHI. Construction of gag-IAPol fusion was achieved via three-fragment ligation involving the PstI-BstEII gag digestion fragment, the BstEII/BamHI digested PCR product and long PstI/BamHI V1R-FLpol backbone fragment.

The MRKAd5-gagpol adenovirus vector was constructed using the BglII fragment of the V1R-gagpol containing the entire ORF of gag-IAPol fusion gene.

## EXAMPLE 30

## Immunogenicity Studies in Non-Human Primates

Cohorts of three (3) macaques were immunized with 10e8 or 10e10 viral particles (vp) of one of the following MRKAd5 HIV-1 vaccines: (1) MRKAd5gag; (2) MRKAd5pol; (3) MRKAd5nef; (4) a mixture containing equal amounts of MRKAd5gag, MRKAd5pol, and MRKAd5nef, or (5) a mixture of equal amounts of MRKAd5gagpol and MRKAd5nef. The vaccines were administered at weeks 0 and 4.

The T cell responses against each of the HIV-1 antigens were assayed by IFN-gamma ELISpot assay using pools of 20-aa peptides that encompass the entire protein sequence of each antigen. The results (Table 25) are expressed as the number of spot-forming cells (sfc) per million peripheral blood mononuclear cells (PBMC) that respond to each of the peptide pools.

Results indicate the following observations: (1) each of the single gene constructs (MRKAd5gag, MRKAd5pol, or MRKAd5nef) is able to elicit high levels of antigen-specific T cells in monkeys; (2) the single-gene MRKAd5 constructs can be mixed as a multi-cocktail formulation capable of eliciting very broad T cell responses against gag, pol, and nef; (3) the MRKAd5 vector expressing the fusion

protein of gag plus IA pol is capable of inducing strong T cell responses to both gag and pol.

**Table 25. Evaluation of Mixtures of MRKAd5 vectors expressing humanized HIV-1 gag, pol, gagpol, nef in rhesus macaques**

5

Grp #	Vaccine T=0, 4 wks	Monk #	T=6 wks				
			Mock	Gag H	Pol - 1	Pol - 2	Nef
1	MRKAd5 gag 10 <sup>10</sup> vp	CB9V	0	15	-	-	-
		CD19	0	374	-	-	-
		109H	1	843	-	-	-
2	MRKAd5 gag 10 <sup>8</sup> vp	99D130	1	948	-	-	-
		W277	16	324	-	-	-
		143H	4	595	-	-	-
3	MRKAd5 pol 10 <sup>10</sup> vp	CC1X	4	-	46	256	-
		AW3W	3	-	463	550	-
		AV43	6	-	95	1333	-
4	MRKAd5 pol 10 <sup>8</sup> vp	AW38	1	-	19	30	-
		CC8K	0	-	50	995	-
		CC21	1	-	33	436	-
5	MRKAd5 nef 10 <sup>10</sup> vp	076Q	9	-	-	-	1204
		091Q	4	-	-	-	85
		083Q	0	-	-	-	176
6	MRKAd5 nef 10 <sup>8</sup> vp	00C029	1	-	-	-	114
		98D022	6	-	-	-	170
		98D160	3	-	-	-	198
7	MRKAd5gag+MRKAd5pol+MRKAd5nef 10 <sup>10</sup> vp each	99D251	3	206	15	193	120
		05H	3	135	21	9	638
		00C016	3	26	4	51	23
8	MRKAd5gag+MRKAd5pol+MRKAd5nef 10 <sup>8</sup> vp each	99D215	1	171	18	193	240
		81H	5	73	6	14	243
		12H	8	1140	115	811	719
9	MRKAd5gagpol +MRKAd5 nef 10 <sup>10</sup> vp each	99D211	0	83	56	838	725
		22H	4	385	119	1194	1915
		61H	4	343	11	765	853
10	MRKAd5gagpol +MRKAd5 nef 10 <sup>8</sup> vp each	34H	3	78	19	5	75
		48H	1	65	105	46	43
		70H	5	158	15	220	191

Indicated are numbers of spot-forming cells per million PBMCs against the peptide pools. Mock, no peptides; gag, H, fifty 20-aa peptides encompassing p55 sequence; pol-1, 20-aa peptides representing N-terminal half of IA pol; pol-2, 20-aa peptides representing the carboxy-terminal half of IA pol; nef, 20-aa peptides encompassing the entire wild-type nef sequence. Responses to the antigens prior to the first immunization did not exceed 40 sfc/10<sup>6</sup> PBMC.

10

## WHAT IS CLAIMED IS

1. A recombinant adenoviral vaccine vector at least partially deleted in  
5 E1 and devoid of E1 activity, comprising:
  - a) an adenovirus *cis*-acting packaging region corresponding to from  
about base pair 1 to between from about base pair 400 to about  
base pair 458 of a wildtype adenovirus genome; and
  - b) a gene encoding an HIV protein or immunologically relevant  
10 modification thereof.
2. A vector in accordance with claim 1 comprising a packaging region  
corresponding to from about base pair 1 to about base pair 450 of a wildtype  
adenovirus genome.
3. A vector in accordance with claim 1 further comprising nucleotides  
15 corresponding to between from about base pair 3511 to about 3524 to about base pair  
5798 of a wildtype adenovirus genome.
4. A vector in accordance with claim 3 comprising base pairs  
corresponding to 1-450 and 3511-5798 of a wildtype adenovirus genome.
5. A vector in accordance with claim 4 which is deleted of base pairs  
20 451-3510.
6. A vector in accordance with claim 1 which is at least partially  
deleted in E3.
7. A vector in accordance with claim 6 wherein the E3 deleted region  
is from base pairs 28,133-30,818.

8. A vector in accordance with claim 1 wherein the gene encoding the HIV protein or modification thereof comprises codons optimized for expression in a human.

9. A vector in accordance with claim 1 wherein the vector comprises a  
5 gene expression cassette comprising:

a) a nucleic acid encoding a protein;

b) a heterologous promoter operatively linked to the nucleic acid encoding the protein; and

(c) a transcription termination sequence.

10 10. A vector in accordance with claim 9 wherein the gene expression cassette is inserted into the E1 region.

11. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette is in an E1 parallel orientation

12. An adenoviral vector in accordance with claim 9 wherein the gene  
15 expression cassette is in an E1 antiparallel orientation.

13. An adenoviral vector in accordance with claim 9 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

14. An adenoviral vector in accordance with claim 13 wherein the promoter is an immediate early human cytomegalovirus promoter.

20 15. An adenoviral vector in accordance with claim 9 wherein the promoter is a murine cytomegalovirus promoter.

16. An adenoviral vector in accordance with claim 9 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

17. An adenoviral vector in accordance with claim 9 wherein the transcription termination sequence is a synthetic polyadenylation signal (SPA).

18. A cell comprising the adenoviral vector of claim 1.

19. Recombinant, replication-defective adenovirus particles harvested  
5 and purified subsequent to transfection of the adenoviral vector of claim 1 into a cell line which expresses adenovirus E1 protein at complementing levels.

20. An HIV vaccine composition comprising purified adenovirus particles of claim 19.

21. An HIV vaccine composition of claim 20 which comprises a  
10 physiologically acceptable carrier.

22. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 1 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant,  
15 replication-defective adenovirus.

23. A method according to claim 22 wherein the cell is a PER.C6<sup>®</sup> cell.

24. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of  
20 claim 21.

25. A method according to claim 24 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

26. A method according to claim 25 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

27. A method according to claim 24 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

28. A method according to claim 24 which comprises administering and readministering the adenovirus vaccine vector to the individual.

29. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV gag or an immunologically relevant modification thereof.

30. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette comprises an open reading frame encoding an HIV gag protein or immunologically relevant modification thereof.

31. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

- a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and
- b) a gene expression cassette comprising
  - i) SEQ ID NO: 29;
  - ii) a heterologous promoter operatively linked to i); and
  - iii) a transcription termination sequence.

32. An adenoviral vector in accordance with claim 31 wherein the gene expression cassette is in an E1 parallel orientation.

33. An adenoviral vector in accordance with claim 31 wherein the gene expression cassette is in an E1 antiparallel orientation.

5           34. An adenoviral vector in accordance with claim 31 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

35. An adenoviral vector in accordance with claim 31 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

10           36. An adenoviral vector in accordance with claim 31 which is at least partially deleted in E3.

37. A cell comprising the adenoviral vector of claim 30.

38. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 30 into a cell  
15   line which expresses adenovirus E1 protein at complementing levels.

39. An HIV vaccine composition comprising purified adenovirus particles of claim 38.

40. An HIV vaccine composition of claim 39 which comprises a physiologically acceptable carrier.

20           41. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 30 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

42. A method according to claim 41 wherein the cell is a PER.C6<sup>®</sup> cell.

43. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of  
5 claim 21.

44. A method according to claim 43 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

10 45. A method according to claim 44 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

46. A method according to claim 43 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

15 47. A method according to claim 43 which comprises administering and readministering the adenovirus vaccine vector to the individual.

48. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV pol or an immunologically relevant modification thereof.

20 49. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette comprises an open reading frame encoding an HIV pol protein or immunologically relevant modification thereof.

50. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and

b) a gene expression cassette comprising

- i) a nucleotide sequence selected the group consisting of SEQ ID NO: 1, SEQ ID NO: 5 and SEQ ID NO: 7;
- ii) a heterologous promoter operatively linked to i); and
- iii) a transcription termination sequence.

51. An adenoviral vector in accordance with claim 50 wherein the gene expression cassette is in an E1 parallel orientation.

52. An adenoviral vector in accordance with claim 50 wherein the gene expression cassette is in an E1 antiparallel orientation.

53. An adenoviral vector in accordance with claim 50 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

54. An adenoviral vector in accordance with claim 50 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

55. An adenoviral vector in accordance with claim 50 which is at least partially deleted in E3.

56. A cell comprising the adenoviral vector of claim 49.

57. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 49 into a cell line which expresses adenovirus E1 protein at complementing levels.

58. An HIV vaccine composition comprising purified adenovirus particles of claim 57.

59. An HIV vaccine composition of claim 58 which comprises a physiologically acceptable carrier.

60. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 49 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

61. A method according to claim 60 wherein the cell is a PER.C6<sup>®</sup> cell.

62. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of claim 59.

63. A method according to claim 62 which further comprises administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

64. A method according to claim 63 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus vaccine.

65. A method according to claim 62 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

66. A method according to claim 62 which comprises administering and readministering the adenovirus vaccine vector to the individual.

5           67. An adenoviral vector in accordance with claim 1 wherein the HIV protein is HIV nef or an immunologically relevant modification thereof.

68. An adenoviral vector in accordance with claim 9 wherein the gene expression cassette comprises an open reading frame encoding an HIV nef protein or immunologically relevant modification thereof.

10           69. A recombinant adenoviral vaccine vector at least partially deleted in E1 and devoid of E1 activity, comprising:

a) an adenovirus *cis*-acting packaging region corresponding to from about base pair 1 to about base pair 450 and from about 3511 to about 5798 of a wildtype adenovirus genome, and deleted for base pairs  
15           corresponding to from about base pair 451 to from about base pair 3510 of a wildtype adenovirus genome; and

b) a gene expression cassette comprising

i) a nucleotide sequence selected the group consisting of  
SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 13 and  
20           SEQ ID NO: 15;

ii) a heterologous promoter operatively linked to i); and

iii) a transcription termination sequence.

70. An adenoviral vector in accordance with claim 69 wherein the gene expression cassette is in an E1 parallel orientation.

71. An adenoviral vector in accordance with claim 69 wherein the gene expression cassette is in an E1 antiparallel orientation.

72. An adenoviral vector in accordance with claim 69 wherein the promoter is a cytomegalovirus promoter devoid of intronic sequences.

5           73. An adenoviral vector in accordance with claim 69 wherein the transcription termination sequence is a bovine growth hormone polyadenylation and transcription termination sequence.

74. An adenoviral vector in accordance with claim 69 which is at least partially deleted in E3.

10           75. A cell comprising the adenoviral vector of claim 68.

76. Recombinant, replication-defective adenovirus particles harvested and purified subsequent to transfection of the adenoviral vector of claim 68 into a cell line which expresses adenovirus E1 protein at complementing levels.

15           77. An HIV vaccine composition comprising purified adenovirus particles of claim 76.

78. An HIV vaccine composition of claim 77 which comprises a physiologically acceptable carrier.

79. A method of producing recombinant, replication defective adenovirus particles containing the adenoviral genome of the adenoviral vector of claim 68 which comprises introducing the adenoviral vector into a host cell which expresses adenoviral E1 protein, and harvesting the resultant recombinant, replication-defective adenovirus.

20

80. A method according to claim 79 wherein the cell is a PER.C6<sup>®</sup> cell.

81. A method of generating a cellular-mediated immune response against HIV in an individual comprising administering to the individual a vaccine of claim 78.

82. A method according to claim 81 which further comprises  
5 administration to the individual a DNA plasmid vaccine, optionally administered with a biologically effective adjuvant, protein or other agent capable of increasing the immune response.

83. A method according to claim 82 wherein the DNA plasmid vaccine is administered to the individual prior to administration of an adenovirus  
10 vaccine.

84. A method according to claim 81 wherein the adenovirus vaccine is preceded by an adenovirus vaccine of a different serotype.

85. A method according to claim 81 which comprises administering and readministering the adenovirus vaccine vector to the individual.

86. A multivalent adenovirus vaccine composition comprising  
15 recombinant, replication-defective adenovirus particles, wherein the adenovirus particles are harvested and purified from a cell line expressing adenovirus E1 protein, and wherein the particles are harvested subsequent to transfection of the cells with an adenoviral vector or vectors in accordance with claim 9; said vector(s) comprising a  
20 gene expression cassette or cassettes comprising nucleotide sequences encoding HIV proteins selected from the group consisting of:

- a) gag, pol, and nef, expressed independently from three individual vectors;

- b) gag, pol, and nef, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- c) gag, pol, and nef, expressed via two vectors, one expressing a pol-nef fusion, and another expressing gag;
- d) gag, pol, and nef, expressed via two vectors, one expressing a gag-pol fusion and another expressing nef;
- e) gag, pol and nef, expressed via two vectors, one expressing a nef-gag fusion and another expressing pol;
- f) gag, pol, and nef, expressed via one vector expressing a gag-pol-nef fusion;
- g) gag and pol, expressed independently from two individual vectors;
- h) gag and pol, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- i) pol and nef, expressed independently from two individual vectors;
- j) pol and nef, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- k) nef and gag, expressed independently from two individual vectors;
- l) nef and gag, expressed independently from one vector with the encoding nucleic acid sequences operatively linked to distinct promoters and transcription termination sequences;
- m) gag and pol, expressed via one vector expressing a gag-pol fusion;

n) pol and nef, expressed via one vector expressing a pol-nef fusion;

and

o) nef and gag, expressed via one vector expressing a nef-gag fusion.

87. A multivalent adenovirus vaccine composition in accordance with  
5 claim 86 wherein the gag-pol fusion consists of SEQ ID NO: 39.

88. A multivalent adenovirus vaccine composition in accordance with  
claim 86 wherein the fused sequences have the encoding nucleic acid sequences  
operatively linked to distinct promoters and transcription termination sequences.

89. A multivalent adenovirus vaccine composition in accordance with  
10 claim 86 wherein the fused sequences have the encoding nucleic acid sequences  
operatively linked to a single promoter; and the encoding nucleic acid sequences  
operatively linked by an internal ribosome entry sequence ("IRES").

Original Adenovector Construct:

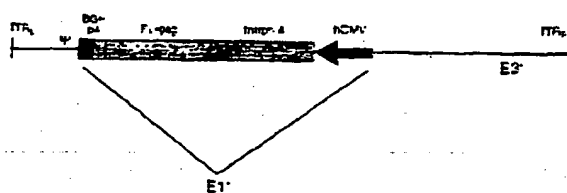


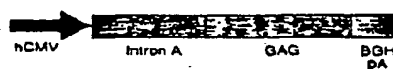
Figure 1: Original HIV-1 gag adenovector.

**Sequence of the open reading frame for FL-gsq (human codon optimized)**

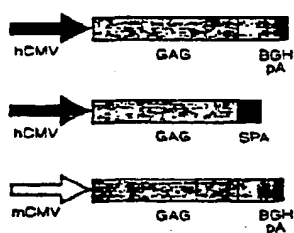
atgggtgctagggtctgtgctgtctgggtgagctggacaagtgaggagaagatcaggctgaggcctgggtg  
caagaagaagtacaagctaaagcacatgtgtgggctccaggaggctggagagggttctgtgaaccctggc  
ctgtggagacctgtgagggtgaggcagatcctgggccaagctccagccctccctgcaaacagggtctgagg  
agctgagggtccctgtacaacacagtggtctacctgtactgtgtgcaccagaagattgatgtgaaggacaccaag  
gaggccttggagaagattgaggaggagcagaacaagtcgaagaagaaggcccagcagggtgtgtgtggc  
acaggcaactccagccagggtgtccagaactacccattgtgcagaacctccagggtccagatggtgtcaccag  
ggcatctccccccggacctggaatgctgtgggtgaagggtggaggagaaggccttctccctgagggtgatccc  
catgttctgtccctgtgtgagggtgtccacccccaggacctgaacaccatgtcgaacacagtggtggggccatc  
aggctgccatgcagatgtcgaaggagaccatcaatgaggagggtgtgtgagggtgacagggtgtcatcctgtgc  
acgtgtggcccatgtgccccggccagatgagggtgagccagggtgtgtgacattgtgtgacaccctccacct  
ccagggtgagatgt  
cctgtgggt  
ccttcagggt  
ggatgacagagacctgt  
ctgccacctgt  
gt  
gaagacagtgaaagt  
agggt  
ggcaaaatctgt  
cccgagggt  
agctgtacccccgt  
gat (SEQ ID NO: 29)

*Figure 2*

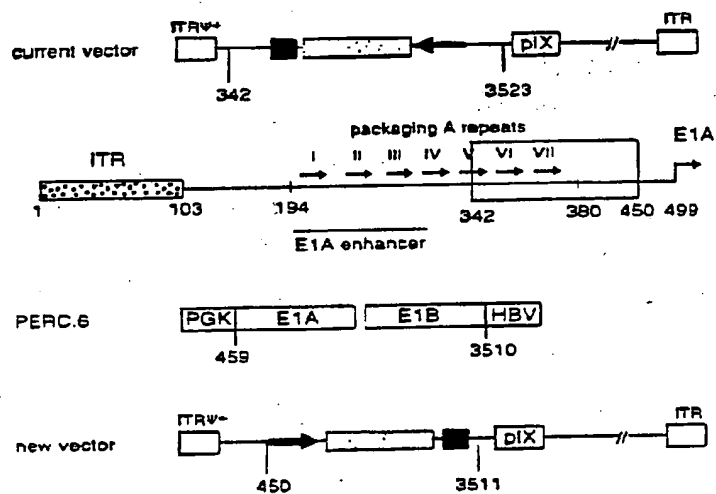
Old Transgene:



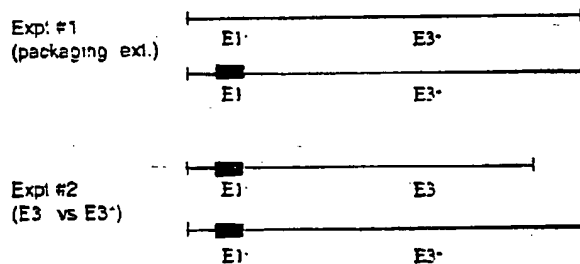
New Transgenes:



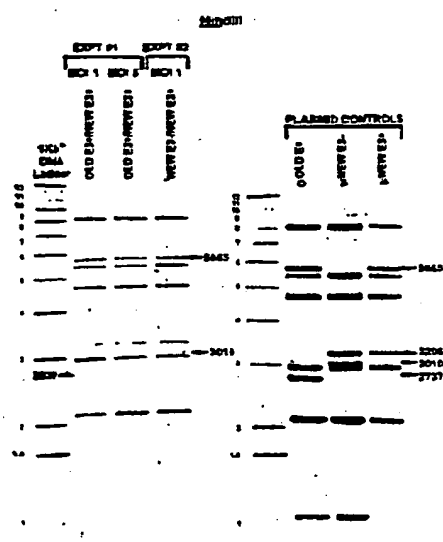
**Figure 3:** Diagrammatic representation of the original HIV-1 gag transgene and the series of new transgene constructions.



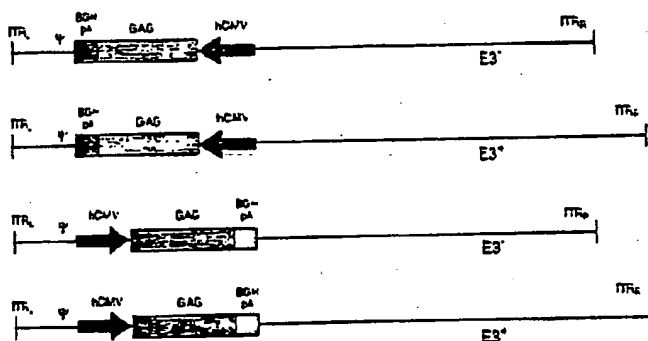
**Figure 4:** Modifications made to the current adenovector backbone in the generation of the new vector.



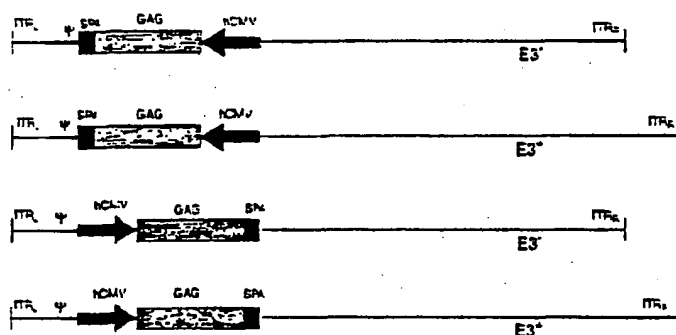
**Figure 5:** Virus mixing experiments to determine the effects of the addition made to the packaging signal region (Expt #1) and analysis of the effects of the E3 gene on viral growth (Expt. #2). The red bars denote the region of modifications made to the E1 deletion.



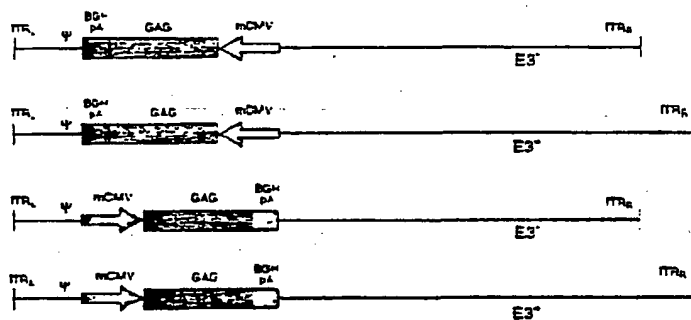
**Figure 6:** Autoradiograph of viral DNA analysis following viral mixing experiments (expts. #1 and #2) as detailed in the text.



**Figure 7A:** hCMV-FLgag-bGHpA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3<sup>-</sup> and E3<sup>+</sup> backbones were constructed.



**Figure 7B:** hCMV-FLgag-SPA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3<sup>-</sup> and E3<sup>+</sup> backbones were constructed.



**Figure 7C:** mCMV-FLgag-bGHpA adenovectors constructed within the "MRK" backbone. E1 parallel and E1 antiparallel transgene orientation within the E3- and E3+ backbones were constructed.

## Plasmid mixing expt: (orientation)

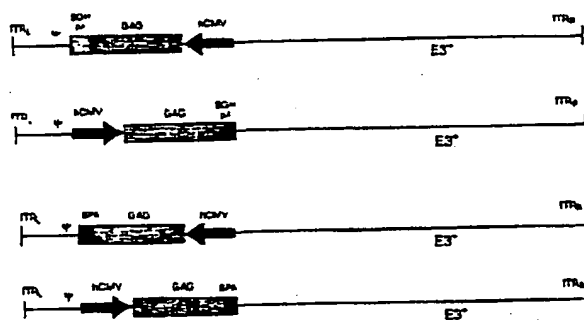


Figure 8A: Effect of transgene orientation

## Plasmid Mixing expt: (poly A signal)

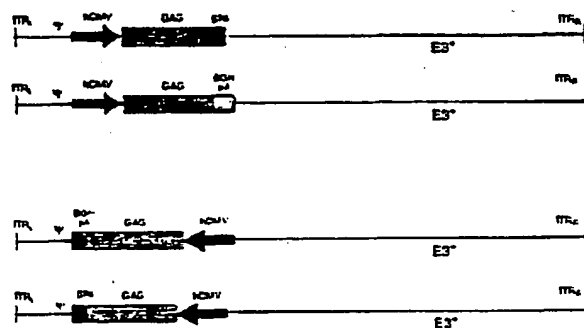


Figure 8B: Effect of polyadenylation signal



Figure 9: Viral DNA from the four Adgag candidates at P5, following BstE11 digestion.

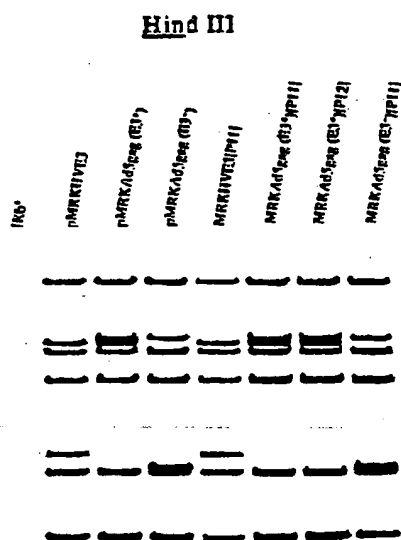
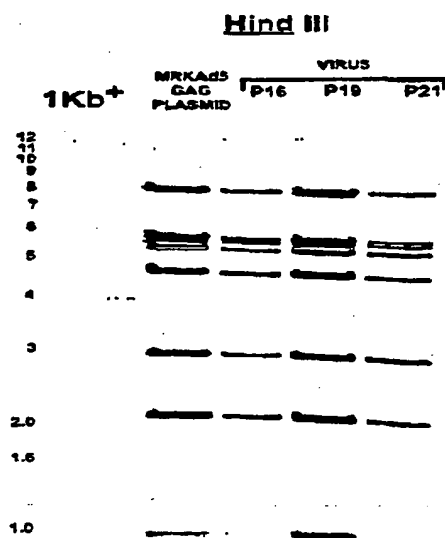


Figure 10: Viral DNA analysis of passage 11 and/or 12 of MRKHVE3, MRKAd5gag and MRKAd5gag(E3-).

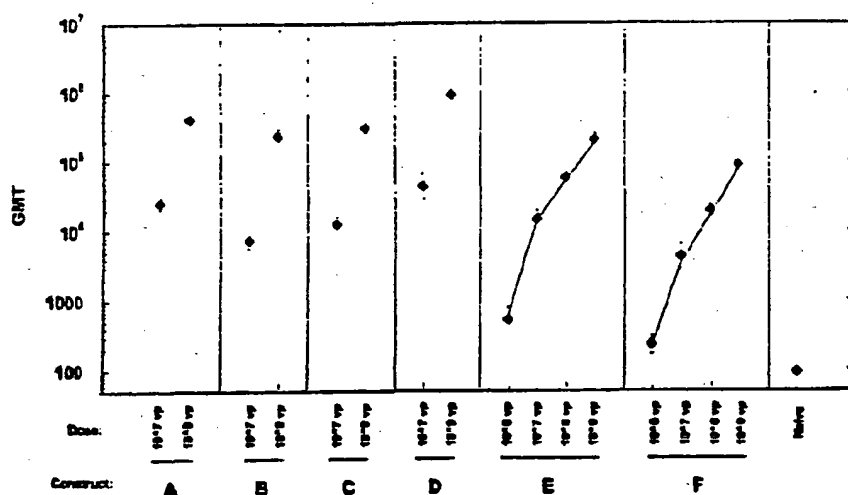


Figure 11: Viral DNA analysis (*Hind*III digestion) of passage 6 MRKHVE3 and MRKAd5gag used to initiate the viral competition study. Last two lanes are passage 11 analysis of duplicate passages of the competition study (each virus at MOI 280 vp).



**Figure 12:** Viral DNA analysis by *HindIII* digestion on high passage numbers for MRKAd5gag in serum containing media with collections made at specified times. The first lane shows the 1 Kb DNA size marker. The other lanes represent pre-plasmid control (digested with Pac1 and *HindIII*), and MRKAd5gag virus continually passaged to P16, P19 and P21 (serum containing media).

13  
**Figure 13.** Serum anti-p24 Levels at 3 Wks post i.m. immunization of balb/c mice (n=10) with Varying Doses of Several Adgag constructs: (A) MRKAd5gag (through passage 5); (B) MRKAd5 E3<sup>+</sup> hCMV-FLgag-bGHpA; (C) MRKAd5 E3<sup>+</sup> hCMV-FLgag-SPA; (D) MRKAd5 E3<sup>+</sup> mCMV-FLgag-bGHpA; (E) research Lot (293 cell-derived) of Ad5HIV-1gag; and (F) clinical lot (Ad5gagFN0001) of Ad5HIV-1gag. Reported are the geometric mean titers (GMT) for each cohort.



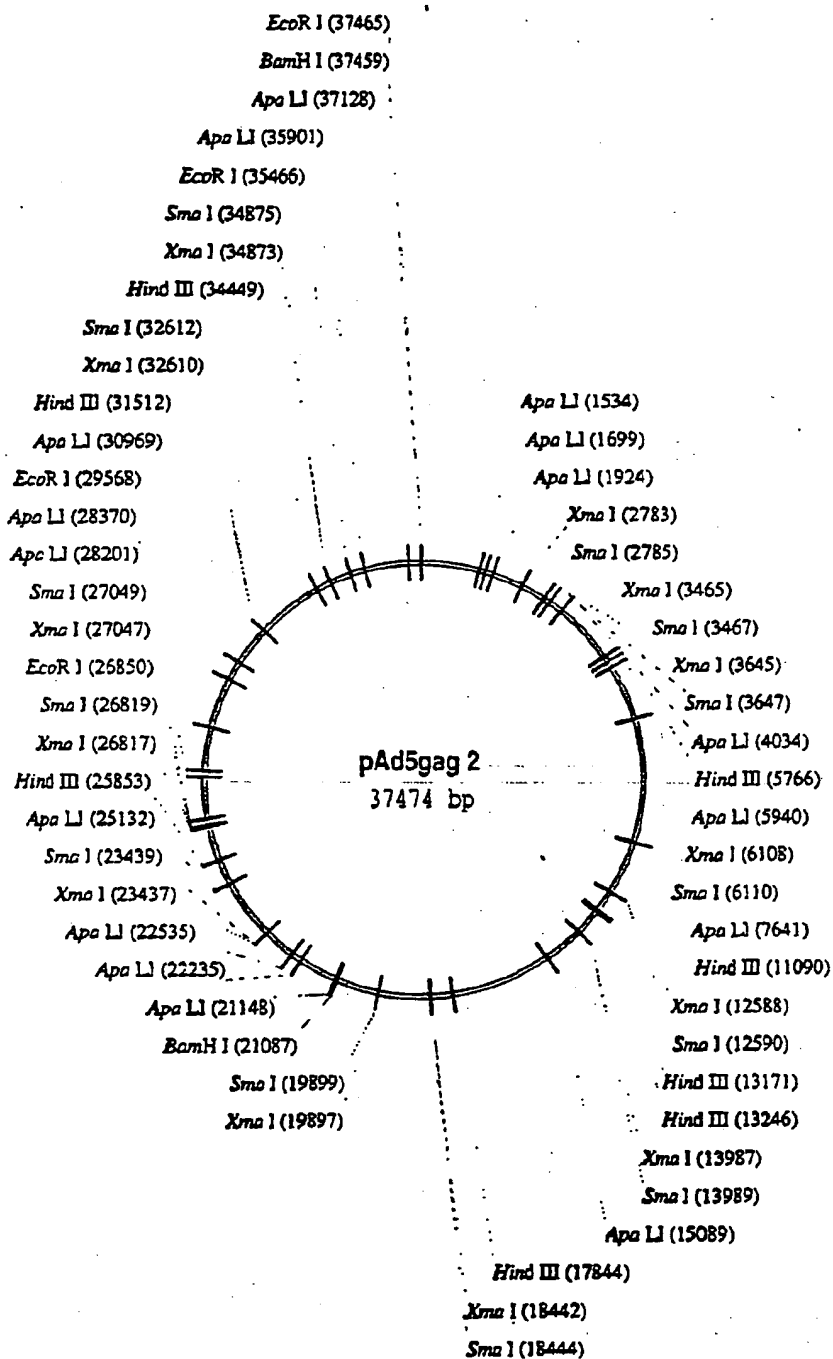


Figure 14

pMRKad599g MEN682

1	TTCTTAATTA ACATCATCAA TAATATATCT TATTATGAT TATATATTA ATGATATTA GCGATGTCG TTTTATAGCT GCGTGGGCG GTGCGNACTG
101	ANGAATTAAT TGTACTAGCT ATTATATGTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
201	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
301	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
401	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
501	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
601	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
701	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
801	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
901	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
1001	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
1101	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
1201	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
1301	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
1401	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
1501	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG
1601	CGCGGCTGAC GTAGTAGTGT GCGGATAGCT TATATATTA ATTAATCTTA ACTTATATTA TACTATTAAT CCGCCACCTC AACAGCTGCA TTTTATAGCT GCGTGGGCG GTGCGNACTG

Figure 1SA

## pMRKAT194at MER62

1701	CACGAGGCGA	TCTGCGCCCG	GACCTGAAAT	GCTGATTTGA	AGTGTGATTC	TTCTCTCTCT	AGGTGATCCC	CATTTCTCT	GCTGTGCTG
1801	GTGCTCCGCT	AGAGGCGGTC	GTGGATCTTA	CGGACCTACT	TTGATGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
1901	AGGCTGCCAC	CCCCAGGAGC	CTGATACCTA	TTGATGATTC	AGTGTGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
2001	TCCGACGCTG	GGGGGCTCTG	GATCTTTTAT	AGGATTTTAT	AGGATTTTAT	AGGATTTTAT	AGGATTTTAT	AGGATTTTAT	AGGATTTTAT
2101	AGGCTGCCAC	CCCCAGGAGC	CTGATACCTA	TTGATGATTC	AGTGTGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
2201	GTGCTCCGCT	AGAGGCGGTC	GTGGATCTTA	CGGACCTACT	TTGATGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
2301	AGGCTGCCAC	CCCCAGGAGC	CTGATACCTA	TTGATGATTC	AGTGTGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
2401	GTGCTCCGCT	AGAGGCGGTC	GTGGATCTTA	CGGACCTACT	TTGATGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
2501	AGGCTGCCAC	CCCCAGGAGC	CTGATACCTA	TTGATGATTC	AGTGTGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
2601	GTGCTCCGCT	AGAGGCGGTC	GTGGATCTTA	CGGACCTACT	TTGATGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
2701	AGGCTGCCAC	CCCCAGGAGC	CTGATACCTA	TTGATGATTC	AGTGTGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
2801	GTGCTCCGCT	AGAGGCGGTC	GTGGATCTTA	CGGACCTACT	TTGATGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
2901	AGGCTGCCAC	CCCCAGGAGC	CTGATACCTA	TTGATGATTC	AGTGTGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
3001	GTGCTCCGCT	AGAGGCGGTC	GTGGATCTTA	CGGACCTACT	TTGATGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
3101	AGGCTGCCAC	CCCCAGGAGC	CTGATACCTA	TTGATGATTC	AGTGTGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC
3201	GTGCTCCGCT	AGAGGCGGTC	GTGGATCTTA	CGGACCTACT	TTGATGATTC	CTCTCTCCCG	AGAGGCGGTC	GTACAGAGA	CGATACGAGC

Figure 15B



pMRKAD5gag MPR682

4901 GATGCGCTTGG AGGCTGATGTC TTCTGATGCT GATGATGTC GCGCTTTGCG CTCTGCTGTC GGGCAGTTGAG CATTGACCA TGGTGTGNTA GTCCAGTCCC  
 CCACCGGAC TCCGACCAAG AGACCAACCA CTTCGCAAGT GGCAGTACAG CCGCTGACATC GTAACTGAT ACCACAGTAT CAGCTGCGGT  
 5001 TCCGCGCGCT GCGCTGATGTC CCGCAGCTTG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 AGCGCGCGCA CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG  
 5101 CCGATTCGCG GATGATGATG TCCGCGCGCG AGGCTGATGTC CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 GCGTAAAGGCC CCGTATGATG TCCGCGCGCG AGGCTGATGTC CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 5201 TCCGCGCGCG CCGTATGATG TCCGCGCGCG AGGCTGATGTC CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 AGGCTGATG CCGTATGATG TCCGCGCGCG AGGCTGATGTC CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 5301 AGAGGCGCTG CCGTATGATG TCCGCGCGCG AGGCTGATGTC CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 TCCTCGGACA GAGCTGCGC ACNAGCTGCG TTTGCTGATG TTTGCTGATG TTTGCTGATG TTTGCTGATG TTTGCTGATG TTTGCTGATG  
 5401 AGTGGGAGCG GTAGCGCTGCG TTTGCTGATG TTTGCTGATG TTTGCTGATG TTTGCTGATG TTTGCTGATG TTTGCTGATG TTTGCTGATG TTTGCTGATG  
 TCACCGCTGCG CATCGCGCGC AGCAGCTGAT CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG  
 5501 GTAGGCTGATG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG  
 CATCGCGCGC CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG  
 5601 CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG  
 CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG  
 5701 CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG  
 GCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG  
 5801 CAGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG CCGCGACCG  
 GTCTGTTGAC CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 5901 CATTGCGGAA AGAGCTGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 GTAGCGCTG TCTGCGGACA CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 6001 GTAGCGCTG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 CATCGCGCGC CAGCGACCG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 6101 AAAGACCGCG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 TTTCTGCGCG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 6201 GCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 6301 ATGTAGGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 TACATGCTG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 6401 CTGCTGCTG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG  
 GACGAGGACA CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG CCGTATGATG

Figure 150

## pMRKd5gag MMR6R2

6501 GCTTCACGCA CBAAGGAGGC GTACAGTCCG CCGAGCTTGT TGAATAGCTT GCGCTGTACC TGACAGTCTA GAGGCACTA GTCCAGGCTT TCCTTGATGA  
 CCGAGTGGCT GCTTCTCTCG CATCTTCAGC GATCTTCAGC AGCTGTACAG CCGCTACCTG AGCTGTACAG CCGCTACCTG AGCTGTACAG CCGCTACCTG  
 6601 TGTCTATACT ATCTGTCTCC TTTTCTTTC ACATCTCTAG GTTGAAGATA AATCTTCTCT AGCTGTACAG CCGCTACCTG AGCTGTACAG CCGCTACCTG  
 TAGGACAGGG AAAAAAAGG TGTCTGAGTC CACTCTCTCT TGTGAAGAGG CCGAGGAGGT CATGAGAGCC TAGGCTTTGG GCAAGCTGAG  
 6701 CBAAGGATAG GAGCTTAGCA TGTATTAATG GTTACAGGTC TGTGAGGAGC AATCTCTCT TGTGAAGAGG CCGAGGAGGT CATGAGAGCC TAGGCTTTGG  
 GCTTCCCATT CTTGATCTCT ACATCTCTAG CACTCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG CCGAGGAGGT CATGAGAGCC TAGGCTTTGG  
 6801 GAGGTGTGGG TBAAGCAAA GGTGTCTCTG ACTATTAATG GTTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT  
 CTCACACACC ACTCTCTCT CACAGGAGC TGTATTAATG ACTCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 6901 CCGTCTCTCT TTTGAGAGC GATTTGAGC AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT  
 GGCAGGAGCA AATCTCTCT CTTAAACCTT CCGCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT  
 7001 TCCGCTACCC TCGGAGAGG TTTTAAATTA CTTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 AGGCTCTCT AGCTCTCT CCAATTAATG GAGCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT  
 7101 GCGATCTCT TGTGAGAGG CAACTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 CCGTACGAGG ACTACCTCT CTTAAACCTT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 7201 GGTGAGAGG CAGGAGAGG CTTGAGAGG CAGGAGAGG TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT  
 CCACTCTCT CTTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 7301 GGTGAGAGG TGTGAGAGG CCGTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 CCACTCTCT CTTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 7401 AACTCTCT CCGGAGAGG TGTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT  
 TGTGAGAGG CCGTCTCT CCGGAGAGG TGTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 7501 GGTGAGAGG GATCTCTCT AACTCTCT CCGGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 CCACTCTCT CTTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 7601 GGTGAGAGG TGTGAGAGG CCGTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 CCACTCTCT CTTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 7701 GGTGAGAGG GATCTCTCT AACTCTCT CCGGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 CCACTCTCT CTTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 7801 GGTGAGAGG GATCTCTCT AACTCTCT CCGGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 CCACTCTCT CTTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 7901 GGTGAGAGG GATCTCTCT AACTCTCT CCGGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 CCACTCTCT CTTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 8001 GGTGAGAGG GATCTCTCT AACTCTCT CCGGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG  
 CCACTCTCT CTTGAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG AATCTCTCT TGTGAAGAGG

Figure 15E

[illegible]

23/144

## pMRKad5qag MER6B2

9701	ACAAAGGCGT GGTATGCGCC GGTGTGATG GGTATGATG AGTGTGCGAT AAGGTGAGTGT TTAAGGTGCT GGTACCGCG GGTACGAGC TCGGTGTAGC TGTGTGCGCA CCAATACCGG GACAACTAC CAAATTAAG TCAACCGATA TTTATGCTGTC AATTTGCGCA CCACTGCGC GACCTCTCTG AGCCACATG;
9801	TGAGACGCGA GTAAAGCGTC GAGTCAAAATTA GTATATGCTT GTAACTATTC ACATATTCG CAAAAATGCG GCGGTGCGCT GCGGTTAGAG; ACTCTGCGCT CATTCGCGG CTCAGTTTAT GCATCAATTA GATTACAGAG TATATCATTA CCAATAGCGT GTTTTTTACG CCGCGCGCGA CCGCAATCTC
9901	GCGCACGCGT AGGTGCGCG GCGCTCGGAG GAGCAATCT TCTAAATATA GCGCATATTA TCGTATGATG TACCTGACAA TCCAGTGAT GCCGCGCGCG CCCGTTCGCA TCCGACCGCG CCGGAGCGCC CCGCTCTAGA AGTTGTATT CCGCTACTAT AGCATCTAC ATGCACTGCT AGTCTCACTA CCGCGCGCGC
10001	GTGTGTGAGG CCGTGTGAGG GTGTGTGAGG CCGTGTGAGG GTGTGTGAGG GTGTGTGAGG GTGTGTGAGG GTGTGTGAGG GTGTGTGAGG GTGTGTGAGG CACCACCTGC GCGCGCTTT CAGCGCTTC GCGCGCTTC GCGCGCTTC GCGCGCTTC GCGCGCTTC GCGCGCTTC GCGCGCTTC GCGCGCTTC
10101	AATGCTGAC GCTCTAGACC GTTCAAAAGG AGACCTGTA AGCTGATCT CTTCTGCTGT CTTGTGATA AATTCGAG GGTATCATG CCGACGACCT; TTAGCAACTG CAGATATCTG CAGCTTTTCC TCTGTGACAT TCGCGCTTA GAGGTACTA GACTACCTAT TTAAAGCTTC CCAATAGTACC GCTGCTGCTP
10201	GCTTCTGAGC CCGTATTCG GCGTCTGCG GTATTCATG CCGTTACCG CCGCTTATG AKCGATGTC TCGGACGTCA GACACCGCG GAGTCTCTCT CCCAAGCTCG GCGCATAGCG CCGCAGCGCG CACTAGTAC GCGATGTCG GTGACACAG TTTGCTCCAC AGCTGTGCTC CTTGTTGCGC CTCACGCGA
10301	TTTGTCTTC TTCAGCGCG GCGGCTGCT GCGTAGCTT TTTGTGAC TATCGCGCG GTCGCACTG CCGATCGAC CCGATCGAC CCGATCGAC AATCCGAAAG AAGTTCGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG
10401	GCTGCTGCG GTATGCGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG CGAGCGAGCG ACATGCGCT TCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG
10501	CTTCTCTCTC TCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GAGCGCGCT ACCTTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG
10601	CGCTCTCTCT TCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGCGAGCG TCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG
10701	CGCGAGCGA TCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG GCGTCTGCG CGCTCTCTCT ACCACTTATG CTTGTGCGCG CTTGTGCGCG CTTGTGCGCG CTTGTGCGCG CTTGTGCGCG CTTGTGCGCG CTTGTGCGCG CTTGTGCGCG
10801	TGAGCGCGAC CCGAGGCTGC AGCTGAGCG GTATGAGCG GTATGAGCG GTATGAGCG GTATGAGCG GTATGAGCG GTATGAGCG GTATGAGCG ACTGCGCGTG GGTCTGCGCG TCGACTTTCG ACTATGCGCA CTCGCGATTC CCGCGAGCG GAGCGTACG TCGCGAGCG TCGCGAGCG TCGCGAGCG
10901	ATCGCGATC GAAGTTTCCA CCGATGCGCG GAGTCTGCG GAGTCTGCG GAGTCTGCG GAGTCTGCG GAGTCTGCG GAGTCTGCG GAGTCTGCG TACGCGCTAG CTTTCAGCT GCTGCGCGCG CTTGAGCGCG TACGCGACTT AGCGCTCGC AAGCGCGCG TCGTCTGCGA ACTGCGCGTG GCGTCTGCG
11001	GATTTAGTCC CCGCGCGCA CAGTGTGCG CCGCGGACCT GTAAAGCGCA TACATACAGA CCGTGAATCA GCGATTAAC TTTCAAAA GCTTTAACAA CTTAATCAG GCGCGCGCG GTGACCGCG GCGCGCTGCA CCAATGCGT ATGCTGCTCT GCGACTTGT GCGTCTGCGA AAGTCTTTT CCAATTTT
11101	CCAGTGTGCT AGCTTGTGCG CCGCGGAGCA GGTGCTTATA GACTGATTC ATCTGCTGCA CTTTGTAGC GCGCTGAGC AATACCGAAA TACGATGCTG GTTGACCGCA TCGCAACACC CCGCGCTCT CCAAGCATAT CCGTACTAG TACGATGCT GATGATGCG CCGCGCTCT TTTTGTGCTT ATGCTTCTGCG
11201	CTCATGCGCG AGCTTCTCT TATATGCGAG CAGATGATG ACAAATGAT ATTCAGCTAT GCGTCTGCA ACATATAGA GCGCGAGCG CCGTGTGCTG GAGTACCGCG TCGACACAGA ATATCAGCT GTGTGCTGCG TGTGCTGCTG TGTGCTGCTG TGTGCTGCTG TGTGCTGCTG TGTGCTGCTG TGTGCTGCTG

Figure 15G

## pMRKAd5gag MER682

11301	TCGATTTGAT	AACATCTCTG	CAGGCTATATG	TGCTATATGGA	GTCTATATTTT	AGCTATATCTG	ACAAATATATG	CGCCATCAAC	TATATCCATCC	TATATCCATCC	TATATCCATCC	TATATCCATCC
11401	AGCTAACTA	TTTCTAGGAC	GTCTCTATATC	ATCACTATCT	CTATATATATC	TTCTATATATC	TTCTATATATC	TTCTATATATC	TTCTATATATC	TTCTATATATC	TTCTATATATC	TTCTATATATC
11501	CAGATTTTAC	CGCCGCAAGA	TATATCCATCC	CGCTATATCT	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC
11601	GTTCMAAATG	CGCCGCTCT	ATATATATATC	GTATATATATC	GTATATATATC	GTATATATATC	GTATATATATC	GTATATATATC	GTATATATATC	GTATATATATC	GTATATATATC	GTATATATATC
11701	ACCTTATAGG	ACCACTATAG	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC	CTATATATATC
11801	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG
11901	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG
12001	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG
12101	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG
12201	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG
12301	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG
12401	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG
12501	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG
12601	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG
12701	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG
12801	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG	CGCTATATAG

Figure 15H



## pMRK415gag MER6R2

14501 CTTACGATTA TCTGAGGCT GTTACATTC CCGACTGCTT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 14601 AGTGGGAGC AACAGAGTC GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 TCGCCGCTG TCTGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 14701 GCGGAGGCT TCGGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 CCGGAGGCT TCGGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 14801 AGAGAGAGC GGTGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 TCTGAGGCT CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 Kpn  
 14901 CTTGAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 15001 TCGGAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 15101 GCTGAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 Ascl  
 15201 CCGGAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 15301 GTGAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 15401 GATAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 15501 AGTAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 TCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 15601 GAGAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 15701 GAGAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 Sfi  
 15801 AGGAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 TCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 15901 AGTAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 TCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 16001 TCGAGGCT AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT  
 AACAGAGTC CCGAGGCT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT GATATGAGT

Figure 15J

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16101	CCAGGTGATC GCGCGGAGG TCTATGTCCT CCGGAGGAG GAGGATGAG ATTACATGCT CTGAAATGCTA ANGCGGTGA AAAAGAGAAA GAAAGATGAT GATCCAGTAG CCGCGCTCT AGATACCGCGT GCGCTCTCTT CTTTCTTCTT TANTCTTCTGAT TTGCGCCACT TTTCTTTTCT CTTTCTACT
16201	GATGATGAGC TTGAGACGA GGTGGAATCT GTTGAACCTA CTCTCTCAG GGAATGATTA CATTGAGGAG GTTGAACCTT AAACGTGTTT TTGGAACCT CTACTACTTG AACTGCTGCT CCACCTTGAC GACGTGATGAT GATGAGGCTT GTCACCTTTC GAGCTGCGCA TTTTGCACAA AACGCTGAG
16301	GACACACGCT AGCTTTTACG CCGCTTACG CACTTACAG CAGCTTATG ATGAGGTGTA GCGCGAGGAG GACCTGCTTG CAGCTGCTTG ACCAGGCAA GTTGTTGCGA TCGAAGATGC GCGCACTCG CAGGATGCTG GTGACATGAC TACTGCTGCT GCGCTGCTG CAGCTGCTG TCGTCTGCTT
16401	CGAGCTCTC GAGGAGTTTG CTTACGGA GCGGATGAG GACATGCTTG CTTTCTTCTT GAGAGGAGT ACCTGACAC CAGGCTTAA GCGCTTAA GCTGCGGAG CCGCTCAAC GATGCGCTTT CCGCTTATTC CTGTACGACC GGAACGCGTA CTTGCTCTCG TTGCTTTG GATGCTTAT CCGGCTATGT
16501	CTGACGAG GCTGTCGCG GCTGTCGCG TCGAGGAA AGGCGGCTT AAGTCTGAG TCTGCTTACT TTGCAACGAC GGTGCACTG ATCTTATCCA GAGTCTGTC AGGACGCGG CAGACGTCG AGCTTCTTT TCGCGCGTA TTCTGCTCT AGACCTGA ACCTGCTG GACGCTGAC TACCATGCT
16601	AGGCGGAGG ACTGATGAT GTCTTGGAAA AATGACGCT GAACTTATG CTGATGCGG CTRGATGCG AGCTGCTGCT GCGGCCAATC MAGCAGTGG CCGCGGACT TCGCGTGC TGACCTTCTA CAGAACCTTT TTTACTGCA CTTTGAATC GACCTCGCG TCCAGGCGCA CCGCGTTAG CCGCGCTGAC GCGGCTGCA
16701	GCGGTGCG AGCTGAGCG TTTGAGATAC CACTTACGTT AGCACATTA TTGCACTGCG CACGAGGCG ATGGAAGAC AACGCTGCG GGTGCTGCT CCAACGAT CGGCGAGCT TCGGACCTG AATCTATG GTCATGCTA TCTGCTCT CAGCTGCTG GTCTCTGCTT ACCCTGCTT TACCTGCTG TTTGCGAGG CCAACGAT
16801	GCGGTGCG AGCTGAGCG TTTGAGATAC CACTTACGTT AGCACATTA TTGCACTGCG CACGAGGCG ATGGAAGAC AACGCTGCG GGTGCTGCT CCAACGAT CGGCGAGCT TCGGACCTG AATCTATG GTCATGCTA TCTGCTCT CAGCTGCTG GTCTCTGCTT ACCCTGCTT TACCTGCTG TTTGCGAGG CCAACGAT
16901	GCGGTGCG AGCTGAGCG TTTGAGATAC CACTTACGTT AGCACATTA TTGCACTGCG CACGAGGCG ATGGAAGAC AACGCTGCG GGTGCTGCT CCAACGAT CGGCGAGCT TCGGACCTG AATCTATG GTCATGCTA TCTGCTCT CAGCTGCTG GTCTCTGCTT ACCCTGCTT TACCTGCTG TTTGCGAGG CCAACGAT
17001	CACCTACGCG CCGAGAGAC GAGCACTAC ACCCTGCTG ACCCTGCTG TCGAGCGGA ACCACTG AGACCTGCG GACGCTGCG CCGCTTACG CCGCTTACG GTGATGCG GGTCTCTG CTTCTGATG GGTGCGGCT TGTGCTGAC CTTGCGGCG GACGCTGCG CCGCTTACG CCGCTTACG CCGCTTACG
17101	GACGCTGCG ACCGAGCTT TCTCTGCTG TCGAGCGGA ACCCTGCTG ACCCTGCTG TCGAGCGGA ACCACTG AGACCTGCG GACGCTGCG CCGCTTACG CCGCTTACG CACGCTGCG ACCGAGCTT TCTCTGCTG TCGAGCGGA ACCCTGCTG ACCCTGCTG TCGAGCGGA ACCACTG AGACCTGCG GACGCTGCG CCGCTTACG CCGCTTACG
17201	ATATGCGCT CACCTGCGCG CTTGCTTTC CCGTCCCGG ATTCCTGTA AGAATGACG GTAGAGGCG CAGGCGCGG CAGGCGCGG CAGGCGCGG CAGGCGCGG TATACCGGA GTGAGCGCG GAGGAGAGG GCGAGCGCG TATGCTCTCT TCTTACTG CATTCTCTG GTACCGCGG GTGCGCGG GCGCGCGG
17301	CGGCTGCG CACGAGCG GCGCGCGG GTGAGCGCG GTGAGCGCG CTAATGCTG CCGCTTACT GCGCTCTCTT ATTCAGCTA TCGCGCGCG GATTCGCGC CGGAGCGCG GTGAGCGCG CCGCGCGG CAGGCTGCG CCGTACGCG CCGCTTACT GCGCTTACT TACGCTGCTT AGCGCGCG CTAACCGCG
17401	GTGCGCGGA TTGATGCTT GCGCTTACG GCGAGAGAC ACTGATTA AACAGTTTC ATGTTGAAA ATCAAAATTA AAGCTGCGA CTCCTACGCT CACGCGCTT AACGTAGGA CCGAGCGT CCGCTCTCT TACTAATTT TGTTCAGG TACACCTTT TAGTTTTT TTTGAGCTT GAGATGCGA
17501	CGCTTCTG TGTACTAT TTGTAGATG GAGGATCA ACTTTGCT TCTGCTG CAGACGCTT CCGCGCTT CAGGCGCG GAGGCGCG TCGCAATTA CGGAGCGG ACATGATTA ACATCTTAC CTTCTGCTT TCGAGCGG AGGCTGAG CAGGCGCG GAGGCGCG GTACCGCTT ACCCTTAT

Figure 15K



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19301	AGACATATAG GGCACACAT CTATGCTCAA CAGGCTAAT TACATGCTT TTATGGA'AA TTTATGCTT CTATGCTAT ACACAGCAC GGTATATATG
19401	TCTTGATTA CCGGTGTTTA GATACGGTIT GTCCGCAATA ATGCTACGAA ATATCTCTTT ANATATACCA GATTACATTA TTTTGTGCTG CCACTTTATC
19501	GGGTGCTGCG CCGGCGCAAC ATGCAAGTTC ATATCTCTTG TACATGCTT ACAGACTCTT GATACAGCTT TTGCTGCTAT TCCATTTGTTT TCCATTTGTTT
19601	CCACAGACC GCGCGGTTCG TAGCGTCAAC TAGCTCAAC CAGCTTCTTA TCTTAATCTT TCTGCTCTTG TCTGCTCTTG TCTGCTCTTG TCTGCTCTTG
19701	ATAGACCAAG GTACTTTTCT ATCTGTAATC AGCTGCTTCA CAGCTTCTTA CAGCTTCTTA CAGCTTCTTA CAGCTTCTTA CAGCTTCTTA CAGCTTCTTA
19801	TATCTTGCTC CATGAAGA TAGACCTTAG TCCGACACT GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA
19901	TTACTGCTTT CCACTGCGAG GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA
20001	ATGACGAA GTGCTACTA CACACTAAT GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA
20101	TTTTCAGATA AAATGCAAT AGAGTTTGA ATATATTTT CAGCTTCTTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA
20201	AAAGTCTAT TTTTACTTA TTCTCAACT TTATTAACCT GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA
20301	TGTATTTGCC GGCACAGCTA AGTTCAGTC TTCTCAACT GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA
20401	ACATAAACGG GCTGTTGAT TTCTATGTCAG GAAGTTTGA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA
20501	CTATGCTGAC TCTTACATTA ACCTTGGTCC AGCTGCTTC GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA
20601	CGATCACTG ACATATTAAT TCGAACCTCG TCGAACCTCG GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA
20701	CGCTCAATGT TCTTGGCAA TGTGCTGCTAT GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA GTGCTACTA
20801	GGGATTTACA ACCAGCCGTT ACCAGGCTTA CAGGGAAGG TGTATGCTCA CAGGGAAGG TGTATGCTCA CAGGGAAGG TGTATGCTCA CAGGGAAGG
20901	ACACTTACGA GTGCAACTTC AGGAGGATG TTATGCTAC TCTTCTCTAC AATGTTACCA AGGATCTCT AGGATCTCT AGGATCTCT AGGATCTCT
21001	TGTGATGCTT CACTTCAAG TCTTCTCTAC AATGTTACCA AGGATCTCT AGGATCTCT AGGATCTCT AGGATCTCT AGGATCTCT AGGATCTCT AGGATCTCT
21101	CATTGCTCTT TACGCTACTT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT
21201	GTAAACCGAA ATGCGGTGGA AGAGGGGTTA CCGGCTGTTG TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG
21301	TATCTCTGCG CCGCTACAT GCTCTACCT ATACCTGCGA TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG
21401	ATAGAGAGGC GCGGTGTTGA CGAGTGGGA TATGCTGCTT TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG TGTGCTGTTG
21501	CTTTCACCGG GGAATTTCTA TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT
21601	TTACTCTCAG CACACTTTA AGAGGCTGCG GTATGCTGTA GTATGCTGTA GTATGCTGTA GTATGCTGTA GTATGCTGTA GTATGCTGTA GTATGCTGTA
21701	AATGCTGTTG GTGCTGMAAT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT TCTTCTCTCT
21801	AAGGCTCAG TTGAGCGGGA GGTTCACAC GGTTCACAC GGTTCACAC GGTTCACAC GGTTCACAC GGTTCACAC GGTTCACAC GGTTCACAC
21901	TTGCGGATTC AACTGCTCTT CCGATGTTG CACGCTCA CACGCTCA CACGCTCA CACGCTCA CACGCTCA CACGCTCA CACGCTCA CACGCTCA
22001	AGGCTCTCTA TATCCACAG AGCTACAGG ACCGATGTA ACCGATGTA ACCGATGTA ACCGATGTA ACCGATGTA ACCGATGTA ACCGATGTA ACCGATGTA
22101	TCCGATGAT ATAGGCTCT TCGATGTTCT TTGCTGATAT TTGCTGATAT TTGCTGATAT TTGCTGATAT TTGCTGATAT TTGCTGATAT TTGCTGATAT
22201	GGATACCAAA CAGGTGGGGA TCTTACACCA ACACACAG TCTTCTCTT TCTTCTCTT TCTTCTCTT TCTTCTCTT TCTTCTCTT TCTTCTCTT
22301	CCTGATGCTT GTCCACCTGT AGGATGCTGT TGTGTTGTTG AGCTTAAAC AATGCTGTA AATGCTGTA AATGCTGTA AATGCTGTA AATGCTGTA
22401	TTCCCTTATC CCGTTATAG CAGACCTCTA TTATGCTGTA TTATGCTGTA TTATGCTGTA TTATGCTGTA TTATGCTGTA TTATGCTGTA TTATGCTGTA TTATGCTGTA
22501	AAAGGATAG GCGATATACC GTTCTGCTGT CACTGCTGT CACTGCTGT CACTGCTGT CACTGCTGT CACTGCTGT CACTGCTGT CACTGCTGT

Figure 15M

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21001	TTATGTCAT GGGGCACTC ACAGACCTG GCCAAGCTT TCTTACTAC ACTGCTGAC ACAGGCTGAG CATGACTTTT GAGGTGATC CCAATGACGA	Flam II
21101	AAATACAGGTA CCCGCTGAG TGCTGTGACC CATTGTTGTA AGAGATGCTA TTCAATGCTG TACGATGACT GTACTGMAAA CTCACCTAG GTTACCTGCT	
	GCCACACCTT CTTTATGTTT TGTTCAGAT CTTTACCTG GTCTGTGTC ACTATGCTCA GTCTGTGTC ATCCAAACCG TGTACCTGCG CAGGCTCTT	
	CGGTGGGAA GAAATACAA ACAAACTCA GAACTGAC CAGGACAGT TGCTGTGCT GGTCTGTGCT GGTCTGTGCT TAGCTGTGCT AC/ TACAGC GTCTGTGCT	EpIII
21201	TGCGCCGCA AGCGACAA ATAAAGAAC AGGCAATC AACAAAGCT GCGCCGCTG GCTTCATGTA GCGGAACTG AAAGCAATG TCAAGATCT	
	AGCGGCGCT TGCGGTGTT TATTTCTTC TGCTGTGAG TTGTTGCTTA CCGGCTTAC CCGGCTTAC GTGCTTAC TTTGCTTAC AGTTCTTAC	
21301	TGTTTGTGG CCATATTTT TGCGCACTA TTACAGGCG TTTCAGCT TGTTTCTCC ACAGAGCTC GGTCTGCTCA TAGCTCAATC GGTCTGCTC	
	ACCAACGCG GTTATMAAA ACCGTGAT ACTGTGCTG AAGTTCTCA AACAAAGG TGTTTCTG GCGAGCGCT ATCAATGAG CCGGCTGCT	
21401	GAGACTGCG GATGCTGCTT GATGCTGCTT GATGCTGCTT GATGCTGCTT GATGCTGCTT GATGCTGCTT GATGCTGCTT GATGCTGCTT GATGCTGCTT	
	CTCTGACCC CCAATGCTG CCAATGCTG CCAATGCTG CCAATGCTG CCAATGCTG CCAATGCTG CCAATGCTG CCAATGCTG CCAATGCTG	
21501	AGTTTACCA GTTGTGCTG GATGCTGCTG GATGCTGCTG GATGCTGCTG GATGCTGCTG GATGCTGCTG GATGCTGCTG GATGCTGCTG	
	TCCAAATGCT CAAATGCTG CAAATGCTG CAAATGCTG CAAATGCTG CAAATGCTG CAAATGCTG CAAATGCTG CAAATGCTG CAAATGCTG	
21601	GCGGCGCAAC TGCGGCTCT GTGCTGCTG GTGCTGCTG GTGCTGCTG GTGCTGCTG GTGCTGCTG GTGCTGCTG GTGCTGCTG GTGCTGCTG	
	CGCGGCTCT GCGGCGCA CCACTGATA GAGGCTGCT GAGGCTGCT GAGGCTGCT GAGGCTGCT GAGGCTGCT GAGGCTGCT GAGGCTGCT	KpnI
21701	CTTATTAAG GGTATACCA CTCATGCTC AACATGCTC AGTATGCTC AGTATGCTC AGTATGCTC AGTATGCTC AGTATGCTC AGTATGCTC	
	GAATATGCT CCAATGCTG GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT	
21801	GCGGCTACTT CCGGAGGCTC AGTGTGCTC AGTGTGCTC AGTGTGCTC AGTGTGCTC AGTGTGCTC AGTGTGCTC AGTGTGCTC AGTGTGCTC	
	GCGGATGTA GCGGATGTA GCGGATGTA GCGGATGTA GCGGATGTA GCGGATGTA GCGGATGTA GCGGATGTA GCGGATGTA GCGGATGTA	
21901	AGGCAATGCT TTTTATTTGT ACATGCTG GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT	
	TGCGGCTGCT TTTTATTTGT TTTTATTTGT TTTTATTTGT TTTTATTTGT TTTTATTTGT TTTTATTTGT TTTTATTTGT TTTTATTTGT	
22001	TGCGGCTGCT GCGGAGGCTC GTTGTGCTG GTTGTGCTG GTTGTGCTG GTTGTGCTG GTTGTGCTG GTTGTGCTG GTTGTGCTG GTTGTGCTG	
	AGCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT	EnfIV
22101	GCGTGTGCTC CATTACCAAC GCGTGTGCTC GCGTGTGCTC GCGTGTGCTC GCGTGTGCTC GCGTGTGCTC GCGTGTGCTC GCGTGTGCTC GCGTGTGCTC	
	CGGACGCTG GTAGTGTGTT GCGAATGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT CCGGCTGCT	
22201	GTGCTGCTC TCGAAGCTA TCGAGGCTG GTGCTGCTC GTGCTGCTC GTGCTGCTC GTGCTGCTC GTGCTGCTC GTGCTGCTC GTGCTGCTC	
	CAGCTGCTG ACCGTGTGAT AGTGTGCTC CAGGCTGCT CAGGCTGCT CAGGCTGCT CAGGCTGCT CAGGCTGCT CAGGCTGCT CAGGCTGCT	
22301	GCGAAGGCTG TCAATGCTG TAGCTGCTT CCGAATGCT CCGAATGCT CCGAATGCT CCGAATGCT CCGAATGCT CCGAATGCT CCGAATGCT	
	CGGCTGCTC AGTTGAACTC ATCGAGGCTA GCGGCTGCT GCGGCTGCT GCGGCTGCT GCGGCTGCT GCGGCTGCT GCGGCTGCT GCGGCTGCT	
22401	CGGCTGCTC GTTATGCTC AGGCTGCTA TTAATGCTT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT GATGCTGCT	
	GCGAAGGCTG CAAATGCTG TCGGCTGCT ATTTGCTGTA CTGAGGCTG CTGAGGCTG CTGAGGCTG CTGAGGCTG CTGAGGCTG CTGAGGCTG	SfiI
22501	GCGGAAAC TGAATGCTG GAGAGGCTG GTGCTGCTG GTGCTGCTG GTGCTGCTG GTGCTGCTG GTGCTGCTG GTGCTGCTG GTGCTGCTG	EpIII
	CGGCTTTG ACTAACGCTC CTGCTGCTG CAGGCTGCT CAGGCTGCT CAGGCTGCT CAGGCTGCT CAGGCTGCT CAGGCTGCT CAGGCTGCT	

Figure 15N

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22601	ATCTTGGCTT TGTGACACTG CTCTCTTACG GCGGCTCTAC CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT TAGAACCCGA ACCATCTGAC GATGATGATG GATGATGATG GATGATGATG GATGATGATG GATGATGATG GATGATGATG GATGATGATG GATGATGATG
22701	GTAGACACTT AGCTTGGCTT TGTGACACTG CTCTCTTACG GCGGCTCTAC CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT CATCTCTGAA TTGACGCGGA AGCTGACACTG CTCTCTTACG GCGGCTCTAC CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
22801	GTAGACACTT AGCTTGGCTT TGTGACACTG CTCTCTTACG GCGGCTCTAC CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT CATCTCTGAA TTGACGCGGA AGCTGACACTG CTCTCTTACG GCGGCTCTAC CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
22901	CATACGCGGG CCAGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT GTATGCGCGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
23001	CCATGCGCTT CTGACGCGGA GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT GTATGCGCGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
23101	CCGACATCCA CCGGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
23201	ACCATTTGTA GCGGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT TGTGACACTG CTCTCTTACG GCGGCTCTAC CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
23301	TTCTTGGGCG ATGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT AGAACGCGGG TTACGCGGGT AGCGGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
23401	CTGACATACC CCGGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
23501	GCACGCGCTC CCGGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT CTGACGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
23601	AGAACGCGGG CCGGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT TTCTCTCTCT GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
23701	GGAGGAGGAA GTGATTTATG AGCAGGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT CTCTCTCTCT CACTAATATG TGTGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
23801	GCAGAGCGAA AGCGCGGGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT CTCTCTCTCT TGTCTCTCTT TTGAGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
23901	GCAGAGCGAA AGCGCGGGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT CTCTCTCTCT TGTCTCTCTT TTGAGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
24001	GCAGAGCGAA AGCGCGGGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT CTCTCTCTCT TGTCTCTCTT TTGAGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA CGTGTCTCTT ATTATCATTA ATGCTTCTCT
24101	TTTTTCCAAA ACTGCGAGAT ACCCTATACC TGTCTCTCTT AGCGGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA ATGCTTCTCT AAAAAGGTTT TGACGTTCTA TGGGATATAG ACCGCGCGGG GATCTCTGAG GTGACACTT CATTCTCTCT GTTCACATCC ATTCTAATTA ATGCTTCTCT

Figure 15D

## pMRAd5gag MER6R2

24201 CTTGGCTCAA GAAAGTGGCA AAATCTTTTG AGGTTCTTTG AGGTTCTTTG CANACTCTTT GCMACAGGAA AACAGCGGAA ATGAAATCTA  
 GAGGAGGTT GCTTCAGGTT TTTTAGAAGC TCCAGGATTC TTAGTATATC TTGATGTC GTTGTGCTT TGTGCTTT TACTTTTCACT  
 24301 CTTGGAGTGG TTTGGGAG TCCAGGCTCA CAAAGGCTTT CTATGCTTAC TAAATGCTAC GATGAGTTC ACCACTTTT CTTACCCGCG ACTTAACTTA  
 GAGACTCTAC AACCACTTTG AGCTCCCACT GTTGGGCTCG GATGAGTTC TTAGCTCCAG TGGGTGAAAC GANTGGGCG TGAATTGGAT  
 24401 CCGCCCAAGG TCAATGAGAC AGTCAATGAGT GATGAGTTC TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG  
 GCGGGCTTCC AGTACTGCTG TCAATGAGT GATGAGTTC TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG  
 24501 TACCGGCACT TCGGAGGAG CAGTATGCTC GCTGCTTCA TAACTGCTG GATGAGTTC TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG  
 ATGCGGCTCA ACCGCTGCTC GTGATGCTG CAGGCTGCTC TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG  
 24601 TACCGTGGAG CTTGAGTCA TCGGCTGCTT CTTGCTTAC CCGGATGCT ACCGATGCT AGGATGCT TTAGCTCCAG TTAGCTCCAG  
 ATGCGGCTC GATGCTGCTT AGCTGCTCA GATGCTGCT GCGCTGCTC TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG  
 24701 CCGGAGGCTT GCAAGATCTC CAAAGTGGAG CTTGCTTAC TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG  
 GCGGCTGCTC CTTGCTTAC CTTGCTTAC CTTGCTTAC CTTGCTTAC TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG  
 24801 CCGCTCAAGG GAGGCTGCTC CCGGCTTAC TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG  
 GCGGCTGCTC CTTGCTTAC CTTGCTTAC CTTGCTTAC CTTGCTTAC TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG TTAGCTCCAG  
 24901 GAGGAGTGGT AACCTCAAGG AGCTGCTCA ACTGCTTAC CAACTTCA ACTGCTTAC CAACTTCA ACTGCTTAC CAACTTCA  
 CTTGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 25001 GATGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 CTTGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 25101 AGGCTCAGG ATCTTGGCTC GCGCTGCTT GCGCTGCTT GCGCTGCTT GCGCTGCTT GCGCTGCTT GCGCTGCTT GCGCTGCTT  
 TCGGAGTGGT TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 25201 CTTGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 GAGGAGTGGT GATGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 25301 ACCGCTGCTC CTTGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 TCGGAGTGGT GAGGAGTGGT GAGGAGTGGT GAGGAGTGGT GAGGAGTGGT GAGGAGTGGT GAGGAGTGGT GAGGAGTGGT  
 25401 CCGCTGCTC GTTGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 GCGGAGTGGT CAACTTGGT TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 25501 AGACCAATCC CCGCTGCTC ATGCTGCTC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 TCGGAGTGGT GCGGAGTGGT TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 25601 TTTGCTTAC GAGGAGTGGT GCGGAGTGGT TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC  
 AAGGAGTGGT CTTGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC TTAGCTTAC

Figure 15P



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27301 CCTCCGCGCC ACTATCCGGA TCAGTTTNTT CTTACTTTTG AGCTGTGTA GACCTGCGG GACGCTAGC ACTGAATGTT AGTGTGAGG GCAGACGAC  
 GAGGCGCGCG TGTATGCGCT AGTTAATATA GATTAGAAC TGTGTTATTT CCGTACGCTG CCGCTGATTC TACTTTTACA TTACCTCTCT GGTCTGTTT  
 27401 TCGCCCTGAA ACACCTGCGC CACTGTGCGC GCACAGATG CTTTCTCCGC GACTCTGCTG ACTTTGCTTA CTTTGAATTT CCGGAGATC ATATCTAGAT  
 ACGCGGACTT TGTGAGACCG GTGACAGCG CGGTGTTCAC GAAATGCGG CTGAGCCAC TCANAGAT GAACCTTAC GGCCTCTTNG TATAGCTCT  
 27501 CCGGCGCAC GCGGTGCGC TTACCGCGA GCGAGAGCTT GCGCTTACG GCGCTTACG TCAATTCGGA GTTTACCCAG CCGCCCGCTG TADTTGAGCG GCAGACGGA  
 GCGCGCGCTG CCGCAGCGCG AATGCGCGT CCGCTCTGAA CCGGCAATCG AGTTAGCGCT CAATGCGCT CAATGCGCT ATCAACTGCG CCGTCCCT  
 27601 CCGTGTGCTC TCACCTGTAT TTCCNACTGT CTTACACTGT GATTAGATCA GATTCTTTGT TCGCATCTCT TCGCTGATTA TAATAATAC AGAATTA  
 GCGACACAG ACTGACACTA AACTGTUACA GATTGCGAC CTTATGTAGT TCTAGAACCA ACGGTATAGA CAGGACTCAT ATTATTTATG TCTTTAAT  
 27701 ATATACTGCG GCTCTTATCG CCACTCTGTA ACGTCCACCG TCTTACACCG CCGACGCAAA CCAATGCTGA CTTTACCTCG TACTTTTAC ATCTCTCG  
 TATATGACCG CAGGATAGC GGTAGGACTT TTGCGGTGCG AGAGTGCGC GGTTCGTTT GGTTCGTTT GGTTCGTTT GGTTCGTTT GGTTCGTTT GGTTCGTTT  
 27801 CTGTGATTTA CAACGTTTC AACCGAGCG GATGAGTGT ACTGATGATC CTCTCCGCG CCGCTGATCG TCGCTGATCG TCGCTGATCG TCGCTGATCG  
 GACTTAAT GTTGTCAAG TTGCTGCTG CTCTCTGTA TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG  
 27901 CCGGACACT ACAGTGTGT CACCGCGCG GATGAGTGT ACTGATGATC CTCTCCGCG CCGCTGATCG TCGCTGATCG TCGCTGATCG TCGCTGATCG  
 GCGCTCTGCA TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG TCGCTGCTG  
 28001 AACAGAGGT GAGCTTGA ACGCTTATG GTATTAGCG ATATTAGCG ATATTAGCG ATATTAGCG ATATTAGCG ATATTAGCG ATATTAGCG  
 TTGCTCTCCA CTGATCTT TTGGAATCG CATTATCGC TTTGCGCTG GATGATGATC TTTGCTCTG TTTGCTCTG TTTGCTCTG TTTGCTCTG  
 28101 TCACTGCTCT CTGATGATG GGTGCGGT ATTCTCTG TTTGATCTT ATCTATGCT TTTGATGCT TTTGATGCT TTTGATGCT TTTGATGCT  
 AGTCCAAAGA GATCTTACG CCAACCGCA TAAGAGACG AACACTAGA GAATATAGA GAATATAGA GAATATAGA GAATATAGA GAATATAGA  
 28201 TCGACATTT CATTATTT CAGCTTTTA AACGCTGCG TCGCCACCA AGATGATTTAG GATGATTTAG GATGATTTAG GATGATTTAG GATGATTTAG  
 ACCTGTAAC GTATATACA GTGCAAAAT TTGCGACCG AGCGTGTGT TCTACTATC TCTACTATC TCTACTATC TCTACTATC TCTACTATC  
 28301 GGTACACCG AAGGTGGA TTTTAGGAG CAGCTCTGA ATGTTACAT CCGAGCTGA GCTTATGAT GCTTATGAT GCTTATGAT GCTTATGAT  
 CCGTGTGCG TTTCCACCT AAAATTCCT GGTGCGCAT TACATTTGA GCTTGTGAT GCTTGTGAT GCTTGTGAT GCTTGTGAT GCTTGTGAT  
 28401 ATGAAGCT GCTTATGCG CACAAACA AATGCGCA GTATCTGTT TATCTATTT TATCTATTT TATCTATTT TATCTATTT TATCTATTT  
 TACTTTTGA CAAATAGCG GTGTTTTGT Bst1107i CATTACCTT CATTACCTT CATTACCTT CATTACCTT CATTACCTT CATTACCTT CATTACCTT CATTACCTT  
 28501 CCGGCTAA AGCATAAA CTTTATGTA TACTTTTCCA TTTTAGGAA TGTGCGCAT TACCATGAT TACCATGAT TACCATGAT TACCATGAT  
 GGTCCCATTT TCGATATTT GAAATGAT ATGAATGAT AATATGAT AATATGAT AATATGAT AATATGAT AATATGAT AATATGAT AATATGAT  
 28601 CAAATGCG TGAACAC TCGCTTTC TGTGCGCTG TGTGCGCTG TGTGCGCTG TGTGCGCTG TGTGCGCTG TGTGCGCTG TGTGCGCTG  
 GTTTTACAC ACCCTTTG ACCGTGAG AGGAGTGA GATGATGAT GATGATGAT GATGATGAT GATGATGAT GATGATGAT GATGATGAT  
 28701 GACGAGCT TATTGAGGA AAGAAATG CTTATTTAC TATGTTACA AGCTATTC ACCACTACT GCTTACTCG CTGCTGCA AAGAAATG  
 CCGGCTGAA ATACTCTT TCTTTTAC GATTTAAT GTTCAATGT TCGATTTAG TCGATTTAG TCGATTTAG TCGATTTAG TCGATTTAG  
 28801 AAGGTAGC ATTATATTA GAATAGAT TAAACCGCG GGTCAATTC TCTCTATTC TCTCTATTC TCTCTATTC TCTCTATTC TCTCTATTC  
 TTTTCAATG TAATATTA CTTATCTTA ATTGCGCG CCGTAAAG AGGATTTAG GTTATGAT TTTATGAT TTTATGAT TTTATGAT TTTATGAT

Figure 1SR

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28901 GCGCTACAC CTTGAGTCA GCTTCCTGG ATGTAACAT CTACTTTGG CCAGCAGCTG TCCGCGCGAT TGTTCGAGT CCAACTACAG CCAACCCACTC  
 CCGCATCTGG GAACCTCAGT CCGAAGGATC TACAGTCTTA GACTGAACCC GTTCGCTTAC AGGCGCTCA AGGCGCTCA GCTTGAATGC GCTTGGTATG  
 29001 TAACAGAGAT GACCAACACA ACCAAGCGG CCGCGCTTAC GGTACTTACA GTTCGCTTAC AGGCGCTCA AGGCGCTCA GCTTGAATGC GCTTGGTATG  
 ATTCTCTCTA CTGGTGTGT TGTTCGCGC GCGCGCTTAC GGTACTTACA GTTCGCTTAC AGGCGCTCA AGGCGCTCA GCTTGAATGC GCTTGGTATG  
 29101 CTTCGCGAG TGTGTGTCT CCATAGCTT TATTTTCTA TACTTATTA TATGCTTCT CATCTCTGC CTAAAGCGCA ACGCGCGCG ACCACCCACTC  
 GAACCCGTAC ACCACCAAGA GTATGCGGA ATACCAACAT ACAGTAAT ATATACATG GACCGACTG AACACATGT TCTTTCTCT TACAGTATGA TTAAATGAGA  
 29201 TATAGTCCCA TCATTGTCT ACACCCAAAC AATATATTA TGTATAGAT GTACCGACTG AATACATGT TCTTTCTCT TACAGTATGA TTAAATGAGA  
 ATATCAGGOT AGTAACAGA TGTGGGTTG TTACTACTT AGTATCTTA CCGCGCTGAC TTGTGTACA AGAAGAGAGA ATGTCTACT AATTACTCT  
 29301 CATGATCTT CAGTTTTTA TATTACTGAC CTTGTGCG CTTTCTGCG ATGCGTGG CCGCTCTAC TCGAAGTGA CTGCTTC A  
 GTACTAAGGA GCTCAAAAT ATATGACTG GACACACCG GAAACACG GCGCGCTG TACCGCGCG CAAGAGTGT AGCTTCACT GACGTAAAT  
 29401 GCTTCACAG TCTATTGCT TTACGATTT GTACCCCTCA GCTCATCTG CAGCTCTATC ACTGTGCTA TCGCTTTAT TCGCTTTAT GACTGCTCT  
 CGAAGTGT CAGTAACGA AATGCTTAA CAGTGGAGT GGTAGTACG GTTGTAGT TCGACCACT ACCGGAATA GGTACGTTA CTGACCCGCA  
 29501 GTTGTGCTT TGCATATCT AGACACCAT CCAAGTACAG GGCAGGACT ATAGCTAGC TTCTTATTA TCTTATTA TGAATTTAC TGTGCTTT  
 CACACCGGA AGTATAGAG TCTGTGCTAG GGTCTATCT CCGTCTCTA TTGCACTCT AGAATCTTA AGAATTTAT ACTTTAATG ACTGTAATA  
 29601 CTGCTGATTA TTGCACTCT ATTGTGCTT TGTGCTGCA CCGCAAGC TATAGACAT ATATACAGA GATTCACCTG TATATGAGT ATTECACTT  
 GACCACTAT AATGTGGA TAGACCGGA ACAGCGGCT GAGGTCTG AGTTCTGTA TATGTAGCT CTAGTACG ATATACCTTA TAAAGTCTA  
 29701 GCTACAAATG AATAAGGAT CTTTCCGAG CCGGTATTA TCGATATG TCTGTGCTG TACCACTTA GCGCTAGCTA TATATCCCA  
 CAGTGTACT TTTTCCCTA GAAAGCTTC GCGCAATAT ACTTATAGT AGCAATATC ACAAGAGCT ATGTAGAT CCGGATGAT ATATAGGAT  
 29801 CTTGACAT GCTGGAAG CAGTATGC CAGTATGC CAGTATGC CAGTATGC CAGTATGC CAGTATGC CAGTATGC CAGTATGC CAGTATGC  
 GAACTGTAA CCGACCTTC GTTATCTAG GTTATCTAG GTTATCTAG GTTATCTAG GTTATCTAG GTTATCTAG GTTATCTAG GTTATCTAG GTTATCTAG  
 29901 CCAAGCANT AGCTTCTCC ACCCTCTCC AATCAGCTA CTTTAACTA ACAGAGAGAG ATGACTGCA CCGTATCT AGAATTTAC AGAATTTAC  
 GGTGCTTAC TCGAGCGGG TCGAGCGGG TCGAGCGGG TCGAGCGGG TCGAGCGGG TCGAGCGGG TCGAGCGGG TCGAGCGGG TCGAGCGGG  
 30001 GAAATATTA CAGAGAGAG CCGCTGAGA AGAGAGAG CAGCGCGCA GCGAGCGCA GCGAGCGCA GCGAGCGCA GCGAGCGCA GCGAGCGCA  
 CTTTATAT GTCTGTGCG GAGGATCTT TCTGCGTCC GTGCGCGCT GTTGTGCTG TACTTATTC TCGAGCTCT GATCCAAATG AACTGCTCA  
 30101 CCAAGCGG TATCTTTGT CTCTTAAAG AGCGCAAGT CACTAGGAC AGTATACCA CCGGACACCG CTTTACTAC AGTTTCTCA CCAAGCTTA  
 CTTTTTCCC ATAGAAACA GAGCAATTC TCGCTTCTA CCGCTTCTG TCGCTTCTG TCGCTTCTG TCGCTTCTG TCGCTTCTG TCGCTTCTG  
 30201 GAAATGAGT GCAAGGAG GAGAAAGCT CATTACCTA ACTGACAT CATTGACAT CATTGACAT CATTGACAT CATTGACAT CATTGACAT  
 CTTTACCAC CAGTACCAC CTTTCTG GAAATGAGT TCACTTCTA GCACTTCTG GCACTTCTG GCACTTCTG GCACTTCTG GCACTTCTG GCACTTCTG  
 30301 CTCTGACCC TATTTAGAG CCGTGTGCT TCAAAATC TATTTCTT TACTATTA AATAATTA TAAAGTCA CTTACTTAA ATCAGTTAGC  
 GAGAGCTGG AATAATCT GAGTCTCT GAGTCTCT GAGTCTCT GAGTCTCT GAGTCTCT GAGTCTCT GAGTCTCT GAGTCTCT

Figure 155

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30401 AATTTCTGT CAGTTTATT CAGACGACC TCTTTGCTT CTTTCAGGT CTGTATTGG AGCTTCCTCC TGGCTGCAAA CTTCCTCCAC ATCTTAAATG  
 TTTAAGACA GGTCAATTA GTCTGCTGG AGCAACGGGA GCAATCTCA GACTATPAG TTGAGGAGG ACCGACCTTT GAGAGGGT TTAGATTATC  
 30501 GAAATTCAGT TTCTCTCTGT TCTGTCCAT CCGACCCAC TATCTTCAG TTGTCTGTA TGAAGGCGC AAGACCGTCT CAGCATACCT TCAALCTCTT  
 CTACAGTCA AAGAGGACA AGATANGTA GGTGTGTTT ATGAAATGTC ACATCTGCG TTCTGCGAGA CTTCATAGGA AGTTGGGG A  
 30601 GTATCCATAT GACACGAAA CCGTCTCTCC ACTGTCTCT TTCTTACTC CTCTCTTGT ATCTCCCAT GGTTTTCAG AGATTCCTCC TGGGTACT :  
 CATAGGTATA CTGTGCTTT GCGCAGGAG TTGACACGGA AAGAAATGAG GAGGCAACA TAGGGGTTA CCAAGATTG TCTCAGGGGG ACCCCATCAG

SpII

30701 TCTTTGCGCC TATCGAAC TCTATTACC TCCATAGCCA TCTTTGCGT CAATAAGGC AACTCTCTT CTCTGAGGA GCGCGGCAC CTTACCTCT:  
 AGAAACGGG ATAGGCTTGG AGATCAATGG AGCTTAGCT GTTTTAGCG TTGCGGAGA GAGACCTCTT CCGGCTCTT GANTGAG: I  
 30801 AATATGTAC CACTGTGAG CCACTCTCA AAAAAGCAA GTTAAATTA AACTGTAAA TATCTGACC CCTCACAGT ACCTCAGAG CCTTACTCT  
 TTTTACATT GTACACTCG GTTGAGAGT TTTTGTGTT CAGTTGTAT TTGAGCTTT ATGAGCTGG GAGGTGTCAA TGGATCTTC GGTATAGCA  
 30901 GCTTCGCGC GCACCTCTAA TGTTCGCGG CACACACTC ACCATCAT CACAGCCCC GCTAACCGG CAGCACTCA AACTTAGCAT TCCCAACCA  
 CCGACGGGG CGTGAGAT ACCAGCGGCC GTTGCTGAG TGTAGTTA GTGTGGGG CGATTGGAC GTGTAGCTT TGTANTCTA AGGTGCGT I  
 31001 GAACCCCTCA CAGTCTAGA AGAAAGCTA GCGCTGCAA CACTAGGCC CCAACACC ACCGATAGCA TATCAGTCC TATCCCCCTT TACCCCCCTT  
 CCTGGAGT GTACAGTCT TCTTTGAT CCGAGCTTT CAGTCTCGG GAGTGTGG TGGCTATCT CATGGAATG ATATGACGG AGTGGGGGA  
 31101 TAACTACTG CACTGTAGC TTGGCATTC ACTGTAGCA GCGCATTT ACACAAATG GAAACTAG ACTAAATGTC GGGCTCTCT TCGATGTA  
 ATGATAGCG GTGACCATC AACCGTAC TGAATCTCT CCGTAAATA TGTCTTATC CTCTGATCC TGAATGTA CCGCAAGAA AGTACATTT  
 31201 AGAGACTTA AACTTTGA CCGTAGCAC TGTTCAGT GTACTTTTA ATATACTTC CTTCGAACT AAGGTATCG GAGCTTGGG TTTGTATCT  
 TCTGTGAT TTGTAACT GCAATGTT GCAAGTCCA CACTATAT TATATGAG GAGCTTGA TTTCAATG CTGGAACCC AACTATAT  
 31301 CAGGCAATA TCAACTTAA TGTAGCGA GCAATAGGA TTATTTCTA AACAGNCC CTTTACTCT ATGTATGTA TCCCTTTGAT GCTCAAAAC  
 GTTCCCTTAT AGTTGAAAT ACATCTCT CCGTATCT TACTAAGAT TTGTCTCG GAAATGAC TACATCAT AGCAAACTA CCACTTTT  
 31401 AACTAAATC AAGACTAGA CAGGCTCTC TTTTATATA CTACGCCAC AACTTGATA TTAATACAA CAAAGGCTT TACTTGTGTA GAGCTTCAA  
 TTGATTTAGA TTCTATCT GTCCCGGAG AATATATT GATCGGGT TGTACCTAT TTTTGGGA ATGAAACAT GTCAAGTTT

HindIII

31501 CAATTCGAA AAGCTTAGG TTACTTAG CACTGCCAG GGTGTGAT TTGACCTAC AGCTTAGCC ATTAATGCG GAGATGGCT TGAATTTGTT  
 GTTAGGTTT TTGAACTCC AATTGATTC GTACGGTTC CCACTACA AACTGATG TCGGTATCG TAATTACGT TACTACCGA ACTTAAAGCA  
 31601 TCACTAATG CACCAACAC AATCCCTC AAACAGAAA TTGTCATGG CCTAGATTT GATTCAGCA AGCTATGAT TCCTAAGTA GDACTGCT  
 ATGGAATTAC GTGGTTTGT TTGAGGGAG TTTGTGTTT AACCGTACC GATCTTAAA CTAACTTTGT TCCATACCA AGGATTTGAT CCTTAGCTG  
 31701 TTAGTTTTGA CAGCAGGAT GCAATTACG TAGGAACAA AATATGAT AAGCTACTT TTGTAGCC ACAGCTCA TCTCTTACT GTAGACTAAA  
 AATCAAACT GTGTGTCCA CGTAAATG ATCTTTGT TTTATTTA TTGATTTGA ACACCTGG TGGTGGGT AGAGATTA CATCTGATTT  
 31801 TGCAGAGAA GATCTTAC TCACTTTGT TTACAGAAA TGTXGAGTC TAATATTC TACATTTCA GTTTGGGTG TTAAGGCG TTTGGCTCA  
 AGCTCTCT TTACGATTT AGTGAACCA GATTTGTTT ACACCTGAG TTATGAGCG ATGTCAAT CAAAGCCGC AATTCCTG AAGCCGAGT  
 31901 ATATCTGAA CAGTTCAAG TCTCATCTT ATTAAGAT TTGAGAAA TGATGTGTA CTAAACAT CTCTCTGGA CCAAAATAT T. AACTTTA  
 TATAGACT GTCAAGTTT ACAGTAGAA TATATTCT AACTGCTTT ACTTACGAT CATTTGTTA GGAAGGACT GGTCTTATA ACCTTGAAT

BglII

32001 GAATGAGA TCTTACTGA GGCAGGCT ATACAGCC TGTGTATTT ATCTTACC TATCAGCTTA TCCAAATCT CAGGTAAA GTCCAAAG  
 CTTTACCTCT AGATGACTT CCGTGTGGA TAGGTATGG ACNACTTAA TACGATTGG ATAGCGAT AGGTTTNGA GTGCCATTTT GACGTTTTT

Figure 15T

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32101 TACATTGTC AGTCAGTTT ACTTAACCG AGACAAACT AACTCTTMA CACTAACCAT TACTACTAAC GTTACACAGG AACACGNGA CACACTCTA  
 ATTGTAAACAG TCAGTTCCAA TGAATTGCG TCCTTTTGA TTCTACACTT TCTATCTGTA ATGTATTTG CCAATGTCTC TTCTCTCTCT GTCTTNGAT  
 32201 AGTGCATACT GTATGTCAAT TTCAATCGAC TCTCTCTGCT ACATTAAT TATTTAAATA TTCTGCACAT CCTCTTACAC CATTCCCNV ATTTCCTT  
 TCAGGTATGA GATACAGTAA AGTACCTCG ATCAACCTG ATCTCTTAC CACTTCTTAT TCTCTCTGTA CAGCATATG AAAAGTATG TACAGCTTT  
 32301 AATAAGAAAT GCTTTGCTT ATCTCTTAC CACTTCTTAC TCTCTCTGTA GAAATTTTA ATCTATTTT CATTAGTAG TATAGCCCCA CACACACATA  
 TATTTCTTA GCAACACAA TACAACTG CCAATATAA AGCTTAACT CTTTAACT TCACTTAAATA GTATCTGCTG TATCTGCTGTA GTCTGCTGTA  
 32401 GCTTATACAG ATCAACCTG CTTTAACTA CTTTAACTA CTTTAACTA CTTTAACTA CTTTAACTA CTTTAACTA CTTTAACTA CTTTAACTA  
 CAAATATGTC TACTGCTGTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 32501 GCTGCTCTTA AATACATCA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 GAGACCTGAT TTTCTGCTGTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 32601 ATAACTCTG CCGGACCTG ACTTAACTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 TATTTGAGG GCGGCTGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 32701 AATGACCTG CTACATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 TTTGCTGCTG GATGCTGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 32801 CTTGACGAA TACATGCT CAGTCTGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 GAGCTGCTT ATGCTGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 32901 TCACTTAAT CAGCAGCTA ACTGACCTG TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 AGTCAATTTA GTCTGCTGTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 33001 AATGACCTG GCAATCACT CAGCAGCTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 TTTGCTGCTG GCTGCTGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 33101 CACACACCTG CAGTACCTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 GTGCTGCTG GCAATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 33201 AGGAACTG GACTGACCTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 TCTGCTGCTG CAGTACCTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 33301 CAGTACCTA CAGTACCTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 GCAATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 33401 AATGACCTG CAGTACCTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 TCTGCTGCTG CAGTACCTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 33501 GAGTACCTA GAGTACCTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT  
 CAGTACCTA TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT TATCATGCT

Figure 15U

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33601 CTGAGGCAAA ACCAGGTGCG GCGGTACAA ACATATTCGC GTCTCCGTTC TTCTCCCTTA GATCCCTCTG TGTAGTAGTT GTATTATATC CACTCTCTTA  
 GACTTCGTTT TGTCCACGCG CCGCATCTTT TGTCTAGACG CAGAGGCGAG AGTCCCGAAT CTATCTAGAC ACATATCAAA CATCATATAG GTAGAGATTT  
 33701 AAGCATCCAG GCGCCGCTCG GTCTCGGTTT CTATTGAAAC TCCCTCATGC GCGCTGCTCC TGTATACATC CACACCGGCA GANTAGGCA CACCCAGGCT  
 TTCTGAGGTC CCGCGGGGAC CGAAGGCCAA GATACATTTG AGTAAGTAGG CCGCGACGGG ACTATCTTAG GTGTGCGGT CTATTTCGGT GTGCGTCCGA  
 33801 ACCTACACAT TGGTCTGCG AGTCACACG GCGAGGCGCG GGAAGAGCTG GAACAGGCAAT GTTTTTTTTT TATCTCCAAA AGATTATCCA AAACCTTAAA  
 TGGATGTGTA AGCAGAGCG TCAGTGCTG TGCTCTCCCG CTTCTCCGAC CTCTCTGTA CAAAAAAA ANTAAAGTTT TCTANTAGGT TTTCGAGTTT  
 33901 ATGAGATCT ATTAAATGAA CCGCTCCCG TCCGCTGCG TGTCTMACT CTACAGCAA AGAACAGATA ATGCAATTTG TAAGATGTTG CACATAGCT  
 TACTTCTAGA TAATTCACAT CCGCGAGCG AGCGCAACCG ACCTGTTTGA GATGTCGTT TCTGTCTAT TACCGTAAC ATTCTACAC GTGTTACCGT  
 34001 TCCAAAGCG AAAGCGCGCT CACGTCGAG TCGAGCTAAA GGTAAACCC TTCAAGGTGA ATCTCTCTTA TAAACATTC AACACCTTCA ACCATGCTCA  
 AGGTTTTCCG TTTCGCGGGA GTGAGGTTTC ACTGCAATTT CCGATTTGCG AAGTCCCACT TAGAGGAGAT ATTGTGAGG TCGTGGAGGT TGGTAGCGGT  
 34101 ATAAATCTC ATCTGCGAC CTCTCTATA TATCTTAG CAAATCCGA ATATTAGTC CCGCAATTT AANAATGCG TCCAGAGCG CCTCCAGCTT  
 TTATTAGAG TAGAGCGGT GAAGAGTTAT ATAGAGTTTC GTTTAGGCT TATATTCAG CCGGTAAACA TTTTATAGCG AGGTCTCGG GAGGTGGA  
 34201 CAGGCTCAG CAGGGAATCA TGAATGCAA AATTCAGTT CTTCAAGAG CTGTATAGCA TTCAAAAGCG GAACATTAAC AANAATGCG CGATCCCGTA  
 GTGCGAGTTTC GTGCTTAGT ACTACGTTT TTAACTCCA GGGTGTCTG GACATATCT AAGTTTCCG CTGTAAATG TTTTATGCG GCTAGGCGAT  
 34301 GGTGCTCTCG CAGGCGACG TGAACATAAT CGTGAGGTC TGCAGGAGC AGCGGCGCA CTTCGCGCG CAGAACCAATG ACAAAGAAC CCACACTGAT  
 CCAAGGAGCG GTCCGCGTGG ACTTGTTATTA GCACTTCAG AGTCCCTCG TCGCGCGGT GAGGCGCGG TCGTTGATAC TGTCTCTTG GGTGTGACTA  
 34401 TATGACAGC ATACTGAG 'CTATCTAG CAGGTAAGC CCGATGAG CTGTGTAG ATAAATGCA AGGTCTGCT CAJAAATC/  
 ATACTGTGCG TATGAGCTTC GATAGGATG GTGCGATCG GTCTACATTC GAACAGTA CCGCGCGCTA TATTTAGCT TCCAGAGCA GTTTTATAG  
 34501 GCGAAGCGCT CCGCGMAAA AGAAGGACA TCGTAGTCAI TGTATGAG ATAAAGGAG GTAGCTCGG GAGCCGCGC AGAACAGAC ACCATTTTTC  
 CGTTTTCGA GCGGTTTTT TCTTCTGT AGCATCAGTA CCGTAGGTC TATTTCCGTC CATTCGAGCG CTGTGTGCG TCTTTTCTG TGTAAAGG  
 34601 TCTCAACAT GTCTGCGGT TTCTGCATA AAGACATAT TGTGTTTTT TTTGTAAAT TGTAAATCT CCGACGAT GTTGTCTTT TGTGTGGA  
 AGAGTTTGT CAGACCGCA AAGACATAT TGTGTTTTT TTTGTAAAT TGTAAATCT CCGACGAT GTTGTCTTT TGTGTGGA  
 34701 ATAGGATAA GAGGACTAC GCGCATGCG GCGTACCTG ATAGACTG ATAAAGCA GTACCGTCA TTAAGACA CCGCGAGCG ATGTCCGCG  
 TATTCGTATT CTGCTGATG CCGTACCGC GCGTACCGC GTGTATTCAG ATGCGTCAAT CCGCGAGTA GACCGCTTAT GGTGCTGTC TACAGGCTC  
 34801 TCATATGTA AGACTCGTA ACACATCAT TTGTGATGTC CACTAGTCA ATAGAGGCA AANACATTA ATAGAGGCA AANACATTA AACCTGAA AANCCCTCT GCTAGGCAA ANTAGCACCC  
 AGTATTACAT TCTGAGCCAT TGTGAGTAT TGTGAGTAT TGTGTTTTT TATCTCTCT TATCTGTTAT TTTGTGAGTA TTTGTGAGTA TTTGTGAGTA  
 34901 AGACACAT ACAGCCCGCA TAGAGGTAT ACGAATTA ATAGAGGCA AANACATTA ATAGAGGCA AANACATTA AACCTGAA AANCCCTCT GCTAGGCAA ANTAGCACCC  
 TCTGTTGTA TGTGCGCGGT ATCTCCATA TGTGTTTTT TGTGTTTTT TATCTCTCT TATCTGTTAT TTTGTGAGTA TTTGTGAGTA TTTGTGAGTA  
 35001 TCCGCTGCA GAAACACATA CAGCGCTTC ACAGCGCGAG CCAATAGAT CAGCTTATC AGTAAAGAG AGTAAAGAG AANACATTA AANACATTA  
 AGCGGAGGT CTGTTGTAT GTCCGAGG TGTGCGCTC GGTATTTGTA GTCTGTTGTA GTCTGTTGTA TTTGTGAGTA TTTGTGAGTA TTTGTGAGTA  
 35101 GCGACGAGCT CATCAGTCA CAGTGTAAA AGGCGCAG TGCAGAGCA GTATATATAG GACTAAAAA TGAAGTAAAG GTTAAAGTCC ACJAAAGCA  
 CCGTGTGGA GTTAGTCA GTACATTTT TTCCCGGTC ACCTGCTCT CATATATTC GTGTTTTT ACTGATTC CAAATTCAG TTTTTTTGT  
 35201 CCGAGAAAC CCGACGCGTA CTTAGCGCA GAAAGAGG CCAAAAC CAGACTTCC TCAATGTC ACTTCGTT TCCGAGTTA TCCGACTTCC  
 GGTCTTTTT GGTGCGCTT GGTGCGCTT CTTGCTTC GGTTTTTG GGTTCGAG AGTTTAGCAG TGAAGGCAA AGGTGCGAT GCGTGAAGG

Figure 15V

pMRKad5gag MER682

35301 CATTTTAAAGAAACTACAAAT TCCCAACACA TACAAATTAC TCCCTCTTAA AACCTACCTC ACCGCCCTCC TTCCCTACGCC CTCCCTCCAG TCACAAACTC  
GTAAATATCT TTTGATGTTA AGGTTCTGT ATGTTCAATG ACCGCTATTT TGGATCAG TCCGCGCGGC AGGCTCCGGB AGGCTCCGGB AGGCTCCGGB AGGCTCCGGB

35401 CACCCCTCA TTATCATATT GCTTCAATC CAAATTAAGG TATATTATAG ATATATATAC TACTACATTT TACTTATAG CTAATCTGGA GATCTCCGAC CTACCCBAAG  
GTGGGGAGT AATAGTATA CCGAATTAG GTTTTATTC ATATATATAC TACTACATTT TACTTATAG CTAATCTGGA GATCTCCGAC CTACCCBAAG

35501 CCCATTATGA TTCTTCTCG TTCCGCGGC ATCGGATTC CCGCTTCA GGCCTATGCA GGCCTATGCA GGCCTATGCA GGCCTATGCA GGCCTATGCA GGCCTATGCA  
GGGTATATAT AAGAAGAGC AAGCGCGCG TACGCTAGC GCGCTATGCA GGCCTATGCA GGCCTATGCA GGCCTATGCA GGCCTATGCA GGCCTATGCA GGCCTATGCA

35601 CCGACCAAA GGCAGGAGC GTTAAATAGT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT  
CGCTCTTTT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT

35701 CAGGTGAGCA AACCGAGC GACTATTAAG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG  
CTCCACCGCT TTGGCTGTC GTGATATTT TATGCTCCG AATGAGGAG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG

35801 CTCTCCCT TTCTCCCT GGAAGCGTG GCTCTTCT GCTCTTCT GCTCTTCT GCTCTTCT GCTCTTCT GCTCTTCT GCTCTTCT GCTCTTCT GCTCTTCT  
GACAGCGCA AAGAGGAG CCGTTCCGAC CCGGAAGAG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG

35901 TCCAGCAAC CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT  
ACGTCTTCT GCGCAAGTC GCGCTGCGCA CCGGAAGAG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG ATACCAGCG

36001 CACTGTAC AGATTATGA GAGCGGTA TGTAGCGGT GTTAGCGGT GTTAGCGGT GTTAGCGGT GTTAGCGGT GTTAGCGGT GTTAGCGGT GTTAGCGGT GTTAGCGGT  
GTGAGCAATG TCTTATCT CTGCTCCAT ACATCCGCA CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT

36101 ATCTCGCT TCTGAGGC AGTTACCT CCGAAGAG TCTGAGGC AGTTACCT CCGAAGAG TCTGAGGC AGTTACCT CCGAAGAG TCTGAGGC AGTTACCT CCGAAGAG  
TAGAGCGAG AGACTTCT TCTGAGGC AGTTACCT CCGAAGAG TCTGAGGC AGTTACCT CCGAAGAG TCTGAGGC AGTTACCT CCGAAGAG TCTGAGGC AGTTACCT

36201 ACCAGCGAT TAGCGGCA AATAGGAT CTCAGAGA TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT  
TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT TCTTCTCT

36301 TTGCTCAT AGATTATCA AAGGATCT CACTAGAT GTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG  
AAACAGTAC TCTATAGT TTCTAGAA GTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG TGTGATCTAG

36401 TCACTGAGC ACTATCTCA GCGATCTG TATTCTGT TATTCTGT TATTCTGT TATTCTGT TATTCTGT TATTCTGT TATTCTGT TATTCTGT TATTCTGT  
AGTCACTCG TGTATAGT CCGTACAG ATAAAGCAG ATAAAGCAG ATAAAGCAG ATAAAGCAG ATAAAGCAG ATAAAGCAG ATAAAGCAG ATAAAGCAG ATAAAGCAG

36501 TGGCCCAAT GTGCAATGA TACCCGCA CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT  
ACCGCTCA CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT

36601 CCGTCACT TTCTCCCT CATCCAGT ATTAATGT GCGCGAGC GCGCGAGC GCGCGAGC GCGCGAGC GCGCGAGC GCGCGAGC GCGCGAGC GCGCGAGC  
GAGCTTGA ATAGCGGAG GTAGTCAGA TATTAACA CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT

36701 CTACAGCAT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT  
GATCTCCGA CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT CCGCTTCT

36801 AAGCGGTT AGCTCTCT GTCTCTCT GTCTCTCT GTCTCTCT GTCTCTCT GTCTCTCT GTCTCTCT GTCTCTCT GTCTCTCT GTCTCTCT GTCTCTCT  
TTTCTCCAA TCGAGGAG CAGGAGCT CAGGAGCT CAGGAGCT CAGGAGCT CAGGAGCT CAGGAGCT CAGGAGCT CAGGAGCT CAGGAGCT CAGGAGCT

36901 GTCATGCA CCGTATGA CTTTCTGT CTTTCTGT CTTTCTGT CTTTCTGT CTTTCTGT CTTTCTGT CTTTCTGT CTTTCTGT CTTTCTGT CTTTCTGT  
CAGTACGTA GCAATCTAC GAAGAGAC TACCACTA TACCACTA TACCACTA TACCACTA TACCACTA TACCACTA TACCACTA TACCACTA TACCACTA

Figure 15W

## pMRKad5gag MER682

37001 CACAGCGGA TAATACCGG CCACATAGCA GAACTTTAAA AGTCTCATC ATTCTAAAC GTCTCTGGG GCGAAACTC TCAGGATCT TACTGCTTT  
 GTGTGCCCC ATTATGGGG GGTGTATGCT CTTCAAATTT TACAGTAG TAACTTTTG CACAGAGCC CCTTTTGG AGTTCTTAGA ATGCGAGAA  
 37101 GAGATCCAGT TCGATTTTAC CCACTGTTGC ACTCAATCTA TCTTAAATAT CTCTTACTTT CACCAAGCTT TCTGGGTAG CAAACACGG AGTCCAAAT  
 CTCATAGTCA AGCTACATTC GTTCAGGACT TGGTTGACT AGACTGCTA GAAATGAA GTCTGCTGNA AGACCCACT GTTTTGTCC TCCCGTTTA  
 37201 CCCCCAAAA AGGAAATAAG GCGACACGG AATGTTGTA TACTTAACT CTCTCTTTT CAAATATAT GAGCATTTA TCAGGTTAT TCTTCAATTA  
 CCGCTTTTT TCCCTATTC CCGCTGTCC TTATACACTT ATGACTATCA GAAAGAAAA GTTATATATA CTTCGTAAAT AGTCCANTA ACAGATATTA  
 37301 GCGATACAT ATTGAATGT ATTAGAAAA ATAAACAAT AGGTTTTC GCGATTTTC CCGAAGAT GCGACCTGAC GTCTAGAAA CCATTATTA  
 CCGCTATGTA TAACTTACA TAAATCTTTT TATTGTTTA TCCCAAGC GCGTGTAG GCGCTTTCA CAGTTCTTT GGTAAATAA  
  
 37401 CATACATTA ACCTATAAA ATAGCGTAT CACAGAGCC TTCTGCTTC AAGATTTGA TTCTGATTT TAAT (SEQ ID NO: 27)  
 GTACTGTAAT TCGATATTTT TATCCGATA GTGCTCGGG AAGCAGAG TTCTTACCT AGGCTTAAAT ATTA (SEQ ID NO: 28)

BamHI  
 EcoRI

Figure 15X

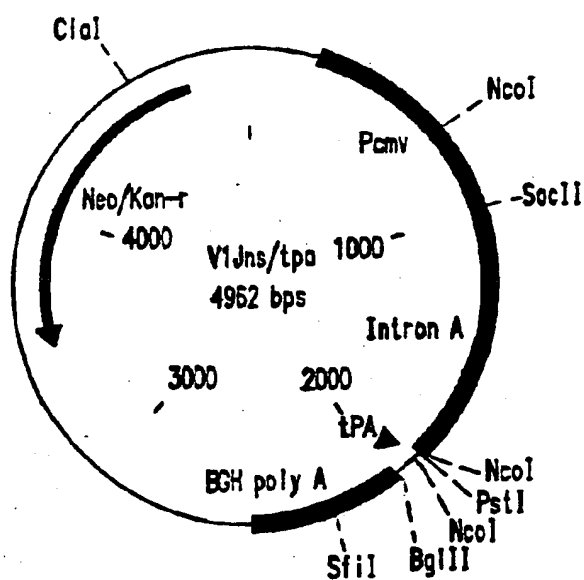
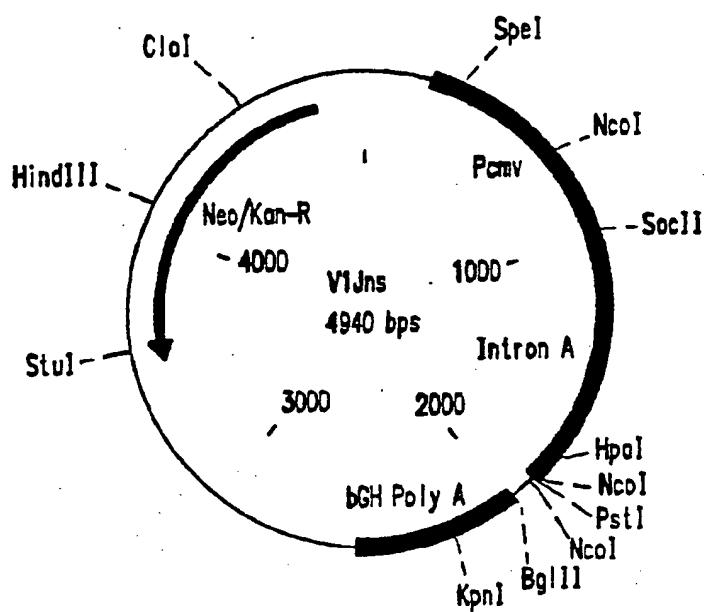


FIGURE 16

AGATCTACCATGGCCCCCATCTCCCCATTGAGACTGTGCCTGTGAAGCTGAAGCCTGGCATGGATGGCCCCAAGGTGAA  
 BgIII MetAlaProIleSerProIleGluThrValProValLysLeuLysProGlyMetAspGlyProLysValLy  
 1 10 20  
 GCAGTGGCCCTGACTGAGGAGAAGATCAAGGCCCTGGTGGAAATCTGCACTGAGATGGAGAAGGAGGGCAAAATCTCCA  
 sGlnTrpProLeuThrGluGluLysIleLysAlaLeuValGluIleCysThrGluMetGluLysGluGlyLysIleSerL  
 30 40 50  
 AGATTGGCCCGAGAACCCTACAACACCCCTGTGTTTGGCATCAAGAAGAAGGACTCCACCAAGTGGAGGAAGCTGGTG  
 ysIleGlyProGluAsnProTyrAsnThrProValPheAlaIleLysLysLysAspSerThrLysTrpArgLysLeuVal  
 60 70  
 GACTTCAGGGAGCTGAACAAGAGGACCCAGGACTTCTGGGAGGTGCAGCTGGGCATCCCCACCCCGCTGGCCTGAAGAA  
 AspPheArgGluLeuAsnLysArgThrGlnAspPheTrpGluValGlnLeuGlyIleProHisProAlaGlyLeuLysLy  
 80 90 100  
 GAAGAATCTGTGACTGTGCTGGCTGTGGGGATGCCTACTTCTGTGCCCCCTGGATGAGGACTTCAGGAAGTACACTG  
 sLysLysSerValThrValLeuAlaValGlyAspAlaTyrPheSerValProLeuAspGluAspPheArgLysTyrThrA  
 110 120 130  
 CCTTCACCATCCCCCTCCATCAACAATGAGACCCCTGGCATCAGGTACCAATGTGCTGCCCCAGGGCTGGAAGGGC  
 loPheThrIleProSerIleAsnAsnGluThrProGlyIleArgTyrGlnTyrAsnValLeuProGlnGlyTrpLysGly  
 140 150  
 TCCCCGCCATCTTCCAGTCCCTCCATGACCAAGATCCTGGAGCCCTTCAGGAAGCAGAACCCTGACATTGTGATCTACCA  
 SerProAlaIlePheGlnSerSerMetThrLysIleLeuGluProPheArgLysGlnAsnProAspIleValIleTyrGl  
 160 170 180  
 GTACATGGCTGCCCTGTATGTGGCTCTGACCTGGAGATTGGGCAGCACAGGACCAAGATTGAGGAGCTGAGGCAGCACC  
 nTyrMetAlaAlaLeuTyrValGlySerAspLeuGluIleGlyGlnHisArgThrLysIleGluGluLeuArgGlnHisL  
 190 200 210  
 TGCTGAGGTGGGGCTGACCACCCCTGACAAGAAGCACCAGAAGGAGCCCCCTTCTGTGGATGGGCTATGAGCTGCAC  
 euLeuArgTrpGlyLeuThrThrProAspLysLysHisGlnLysGluProProPheLeuTrpMetGlyTyrGluLeuHis  
 220 230  
 CCGGACAAGTGGACTGTGCACCCCATTTGTGCTGCCTGACAAGGACTCCTGGACTGTGAATGACATCCAGAAGCTGGTGGC  
 ProAspLysTrpThrValGlnProIleValLeuProGluLysAspSerTrpThrValAsnAspIleGlnLysLeuValGl  
 240 250 260  
 CAAGCTGAAGTGGGCTCCCAAATCTACCCCTGGCATCAAGGTGAGGCAGCTGTGCAAGCTGCTGAGGGGCACCAAGGCC  
 yLysLeuAsnTrpAlaSerGlnIleTyrProGlyIleLysValArgGlnLeuCysLysLeuLeuArgGlyThrLysAlaL  
 270 280 290

FIGURE 17A

TGA CTGAGGTGATCCCCCTGACTGAGGAGGCTGAGCTGGAGCTGGCTGAGAACAGGAGATCCTGAAGGACCTGTGCAT  
 E u T h r G l u V o l l e P r o L e u T h r G l u G l u A l o G l u L e u G l u L e u A l o G l u A s n A r g G l u l l e L e u L y s G l u P r o V o l H i s  
 300 310

GGGGTG TACTATGACCCCTCAAGGACCTGATTGCTGAGATCCAGAAGCAGGGCCAGGGCCAGTGGACCTACCAATCTA  
 G l y V o l T y r T y r A s p P r o S e r L y s A s p L e u l l e A l o G l u l l e G l n L y s G l n G l y G l n G l y G l n T r p T h r T y r G l n l l e T y  
 320 330 340

CCAGGAGCCCTTCAAGAACCTGAAGACTGGCAAGTATGCCAGGATGAGGGGGCCACACCAATGATGTGAAGCAGCTGA  
 r G l n G l u P r o P h e L y s A s n L e u L y s T h r G l y L y s T y r A l o A r g M e l A r g G l y A l o H i s T h r A s n A s p V o l L y s G l n L e u T  
 350 360 370

CTCAGGCTGTGCAGAAGATCACCCTGAGTCCATTGTGATCTGGGGCAAGACCCCAAGTTCAAGCTGCCCATCCAGAAG  
 h r G l u A l o V o l G l n L y s l l e T h r T h r G l u S e r l l e V o l l l e T r p G l y L y s T h r P r o L y s P h e L y s L e u P r o l l e G l n L y s  
 380 390

GAGACCTGGGAGACCTGGTGGACTGAGTACTGGCAGGCCACCTGGATCCCTGAGTGGGAGTTTGTGAACACCCCCCCCCCT  
 G l u T h r T r p G l u T h r T r p T r p T h r G l u T y r T r p G l n A l o T h r T r p l l e P r o G l u T r p G l u P h e V o l A s n T h r P r o P r o L e  
 400 410 420

GGTGAAGCTGTGGTACCAGCTGGAGAAGGAGCCCATTTGTGGGGCTGAGACCTTCTATGTGGCTGGGGCTGCCAACAGGG  
 u V o l L y s L e u T r p T y r G l n L e u G l u L y s G l u P r o l l e V o l G l y A l o G l u T h r P h e T y r V o l A l o G l y A l o A s n A r g G  
 430 440 450

AGACCAAGCTGGGCAAGGCTGGCTATGTGACCAACAGGGGCAGGCAGAGGTGGTGACCTGACTGACACCAACCAACCAG  
 l u T h r L y s L e u G l y L y s A l o G l y T y r V o l T h r A s n A r g G l y A r g G l n L y s V o l V o l T h r L e u T h r A s p T h r T h r A s n G l n  
 460 470

AAGACTGCCCTCCAGGCCATCTACCTGGCCCTCCAGGACTCTGGCCTGGAGGTGAACATTGTGACTGCCCTCCAGTATGC  
 L y s T h r A l o L e u G l n A l o l l e T y r L e u A l o L e u G l n A s p S e r G l y L e u G l u V o l A s n l l e V o l T h r A l o S e r G l n T y r A l  
 480 490 500

CCTGGGCATCATCCAGGCCAGCCTGATCAGTCTGAGTCTGAGCTGGTGAACCAGATCATTGAGCAGCTGATCAAGAAGG  
 a L e u G l y l l e l l e G l n A l o G l n P r o A s p G l n S e r G l u S e r G l u L e u V o l A s n G l n l l e l l e G l u G l n L e u l l e L y s L y s G  
 510 520 530

AGAAGGTGTACCTGGCCTGGGTGCCGCCACCAAGGCCATTGGGGGCAATGAGCAGGTGGACAAGCTGGTGTCTGCTGGC  
 l u L y s V o l T y r L e u A l o T r p V o l P r o A l o H i s L y s G l y l l e G l y G l y A s n G l u G l n V o l A s p L y s L e u V o l S e r A l o G l y  
 540 550

ATCAGGAAGGTGCTGTTCCCTGGATGGCATTGACAAGGCCAGGATGAGCATGAGAAGTACCACTCCAAGTGGAGGGCTAT  
 l l e A r g L y s V o l L e u P h e L e u A s p G l y l l e A s p L y s A l o G l n A s p G l u H i s G l u L y s T y r H i s S e r A s n T r p A r g A l o M e  
 560 570 580

FIGURE 17B

GGCTCTGACTTCAACCTGCCCCCTGTGGTGGCTAAGGAGATTGTGGCTCCTGTGACAAGTCCAGCTGAAGGGGAGG  
 tAlaSerAspPheAsnLeuProProValVolAlaLysGluIleValAlaSerCysAspLysCysGlnLeuLysGlyGluA  
 590 600 610

CCATGCATGGGCAGGTGGACTGCTCCCTGGCATCTGGCAGCTGGCTGCACCCACCTGGAGGGCAAGGTGATCCTGGTG  
 lAlaMetHisGlyGlnVolAspCysSerProGlyIleTrpGlnLeuAlaCysThrHisLeuGluGlyLysValIleLeuVal  
 620 630

GCTGTGCATGTGGCTCCGGCTACATTGAGGCTGAGGTGATCCCTGCTGAGACAGCCAGGAGACTGCCTACTTCTGCT  
 AlaVolHisVolAlaSerGlyTyrIleGluAlaGluValIleProAlaGluThrGlyGlnGluThrAlaTyrPheLeuLe  
 640 650 660

GAAGCTGGCTGGCAGGTGGCTGTGAAGACCATCCACACTGCCAATGGCTCCAACCTTCACTGGGGCCACAGTGAGGGCTG  
 uLysLeuAlaGlyArgTrpProVolLysThrIleHisThrAlaAsnGlySerAsnPheThrGlyAlaThrValArgAlaA  
 670 680 690

CCTGCTGGTGGCTGGCATCAAGCAGGAGTTTGGCATCCCTACAACCCCACTCCAGGGGGTGGTGGCTCCATGAAC  
 lAlaCysTrpTrpAlaGlyIleLysGlnGluPheGlyIleProTyrAsnProGlnSerGlnGlyValVolAlaSerMetAsn  
 700 710

AAGGAGCTGAAGAAGATCATTGGGCAGGTGAGGGACCAGGCTGAGCACCTGAAGACAGCTGTGCAGATGGCTGTGTTTAT  
 LysGluLeuLysLysIleIleGlyGlnVolArgAspGlnAlaGluHisLeuLysThrAlaVolGlnMetAlaVolPheIle  
 720 730 740

CCACAACCTTCAAGAGGAAGGGGGCATCGGGGGCTACTCCGCTGGGAGAGGATTGTGGACATCATTGCCACAGACATCC  
 eHisAsnPheLysArgLysGlyGlyIleGlyGlyTyrSerAlaGlyGluArgIleVolAspIleIleAlaThrAspIleG  
 750 760 770

AGACCAAGGAGCTCCAGAAGCAGATCACCAAGATCCAGAAGTTCAGGCTGTACTACAGGACTCCAGGAACCCCTGTGG  
 lThrLysGluLeuGlnLysGlnIleThrLysIleGlnAsnPheArgValTyrTyrArgAspSerArgAsnProLeuTrp  
 780 790

AAGGGCCCTGCCAAGCTGCTGTGGAAGGGGAGGGGGCTGTGGTGATCCAGGACAACCTCTGACATCAAGGTGGTGGCCAG  
 LysGlyProAlaLysLeuLeuTrpLysGlyGluGlyAlaVolVolIleGlnAspAsnSerAspIleLysVolVolProAr  
 800 810 820

GAGGAAGGCCAAGATCATCAGGGACTATGGCAAGCAGATGGCTGGGGATGACTGTGTGGCTCCAGGCAGGATCAGGACT  
 gArgLysAlaLysIleIleArgAspTyrGlyLysGlnMetAlaGlyAspAspCysVolAlaSerArgGlnAspGluAspx  
 830 840 850

AAAGCCCGGCAGATC (SEQ ID NO: 3)  
 Xx Bg11 (SEQ ID NO: 4)

FIGURE 17C



WT	- ATG GGT GGC AAG TGG TCA AAA CGT AGT GTG CCT GGA TGG TCT	-42
OPT	- ATG GGC GGC AAG TGG TCC AAG AGG TCC GTG CCC GGC TGG TCC	
	M G G K W S K R S V P G W S	-14
WT	- ACT GTA AGG GAA AGA ATG AGA CGA GCT GAG CCA GCA GCA GAT	-84
OPT	- ACC GTG AGG GAG AGG ATG AGG AGG GCC GAG CCC GCC GCC GAC	
	T V R E R M R R A E P A A D	-28
WT	- AGG GTG AGA CGA ACT GAG CCA GCA GCA GTA GGG GTG GGA GCA	-126
OPT	- AGG GTG AGG AGG ACC GAG CCC GCC GCC GTG GGC GTG GGC GCC	
	R V R R T E P A A V G V G A	-42
WT	- GTA TCT CGA GAC CTG GAA AAA CAT GGA GCA ATC ACA AGT AGC	-168
OPT	- GTG TCC AGG GAC CTG GAG AAG CAC GGC GCC ATC ACC TCC TCC	
	V S R D L E K H G A I T S S	-56
WT	- AAT ACA GCA GCT ACC AAT GCT GAT TGT GCC TGG CTA GAA GCA	-210
OPT	- AAC ACC GCC GCC ACC AAC GCC GAC TGC GCC TGG CTG GAG GCC	
	N T A A T N A D C A W L E A	-70
WT	- CAA GAG GAT GAG GAA GTG GGT TTT CCA GTC AGA CCT CAG GTA	-252
OPT	- CAG GAG GAC GAG GAG GTG GGC TTC CCC GTG AGG CCC CAG GTG	
	Q E D E E V G F P V R P Q V	-84
WT	- CCT TTA AGA CCA ATG ACT TAC AAG GGA GCT GTA GAT CTT AGC	-294
OPT	- CCC CTG AGG CCC ATG ACC TAC AAG GGC GCC GTG GAC CTG TCC	
	P L R P M T Y K G A V D L S	-98
WT	- CAC TTT TTA AAA GAA AAG GGG GGA CTG GAA GGG CTA ATT CAC	-336
OPT	- CAC TTC CTG AAG GAG AAG GGC GGC CTG GAG GGC CTG ATC CAC	
	H F L K E K G G L E G L I H	-112
WT	- TCA CAG AAA AGA CAA GAT ATC CTT GAT CTG TGG GTC TAC CAC	-378
OPT	- TCC CAG AAG AGG CAG GAC ATC CTG GAC CTG TGG GTG TAC CAC	
	S Q K R Q D I L D L W V Y H	-126
WT	- ACA CAA GGC TAC TTC CCT GAT TGG CAG AAC TAC ACA CCA GGG	-420
OPT	- ACC CAG GGC TAC TTC CCC GAC TGG CAG AAC TAC ACC CCC GGC	
	T Q G Y F P D W Q N Y T P G	-140

FIGURE 19A

WT	- CCA GGA ATC AGA TTT CCA TTG ACC TTT GGA TGG TGC TTC AAG	-462
OPT	- CCC GGC ATC AGG TTC CCC CTG ACC TTC GGC TGG TGC TTC AAG	
	P G I R F P L T F G W C F K	-154
WT	- CTA GTA CCA GTT GAG CCA GAA AAG GTA GAA GAG GCC AAT GAA	-504
OPT	- CTG GTG CCC GTG GAG CCC GAG AAG GTG GAG GAG GCC AAC GAG	
	L V P V E P E K V E E A N E	-168
WT	- GGA GAG AAC AAC TGC TTG TTA CAC CCT ATG AGC CAG CAT GGG	-546
OPT	- GGC GAG AAC AAC TGC CTG CTG CAC CCC ATG TCC CAG CAC GGC	
	G E N N C L L H P M S Q H G	-182
WT	- ATA GAG GAC CCG GAG AAG GAA GTG TTA GAG TGG AGG TTT GAC	-588
OPT	- ATC GAG GAC CCC GAG AAG GAG GTG CTG GAG TGG AGG TTC GAC	
	I E D P E K E V L E W R F D	-196
WT	- AGC AAG CTA GCA TTT CAT CAC GTG GCC CGA GAG CTG CAT CCG	-630
OPT	- TCC AAG CTG GCC TTC CAC CAC GTG GCC AGG GAG CTG CAC CCC	
	S K L A F H H V A R E L H P	-210
WT	- GAG TAC TAC AAG GAC TGC TGA (SEQ ID NO:30)	-651
OPT	- GAG TAC TAC AAG GAC TGC TAA (contained within SEQ ID NO:9)	
	E Y Y K D C (SEQ ID NO:10)	-216

FIGURE 19B

**FIGURE 20**

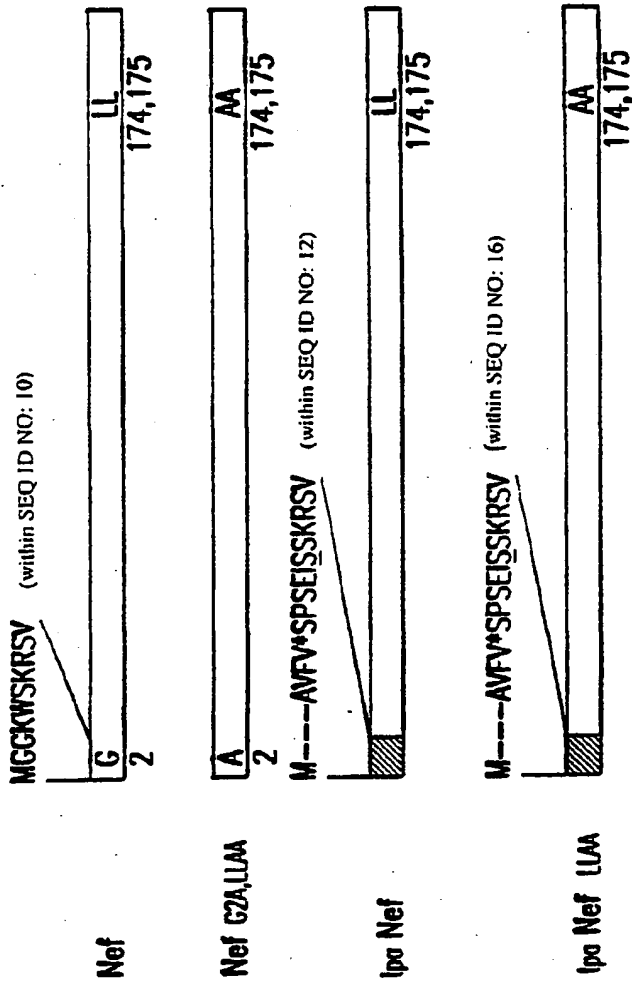


FIGURE 21

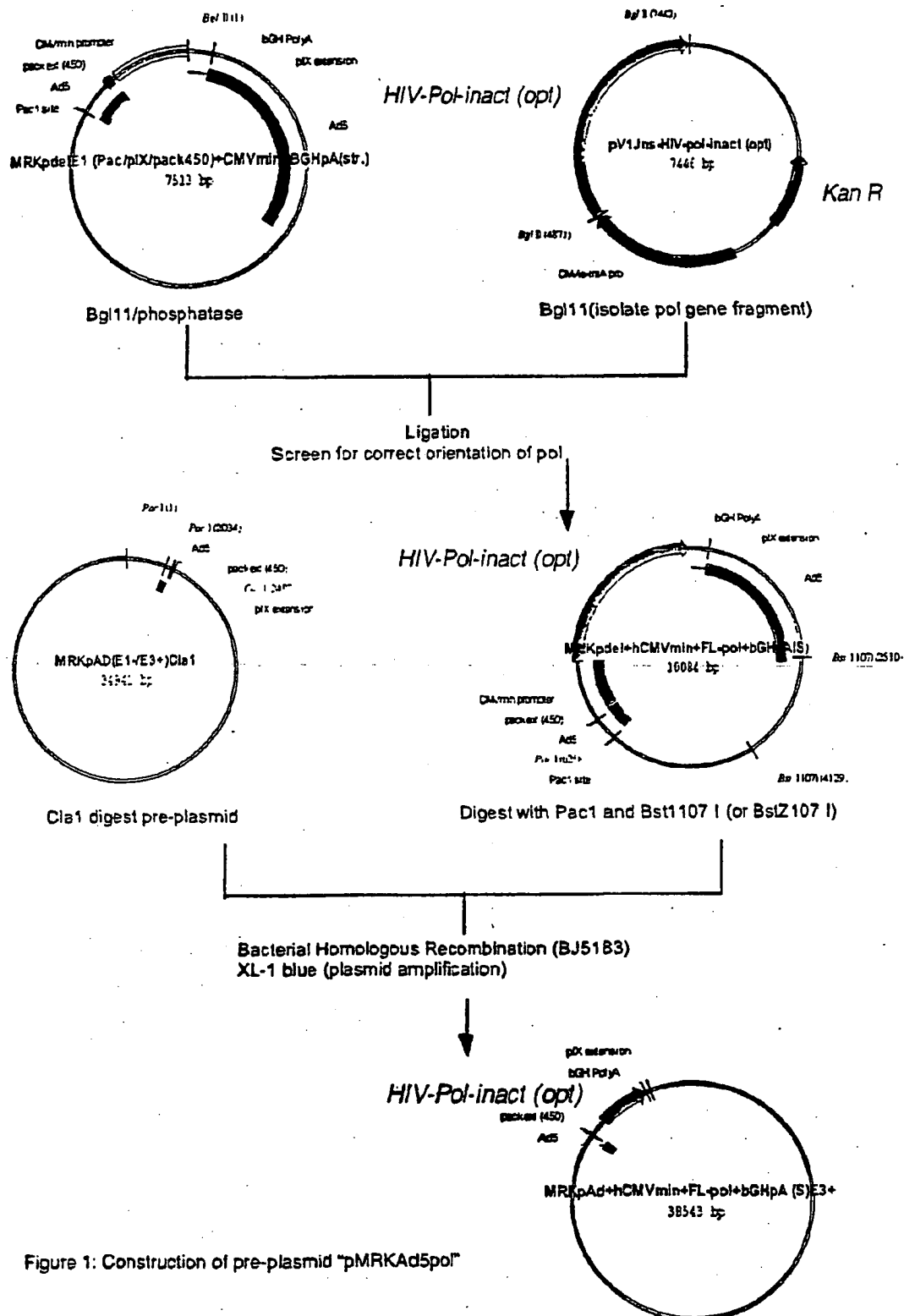


Figure 1: Construction of pre-plasmid "pMRKAd5pol"

**FIGURE 22**

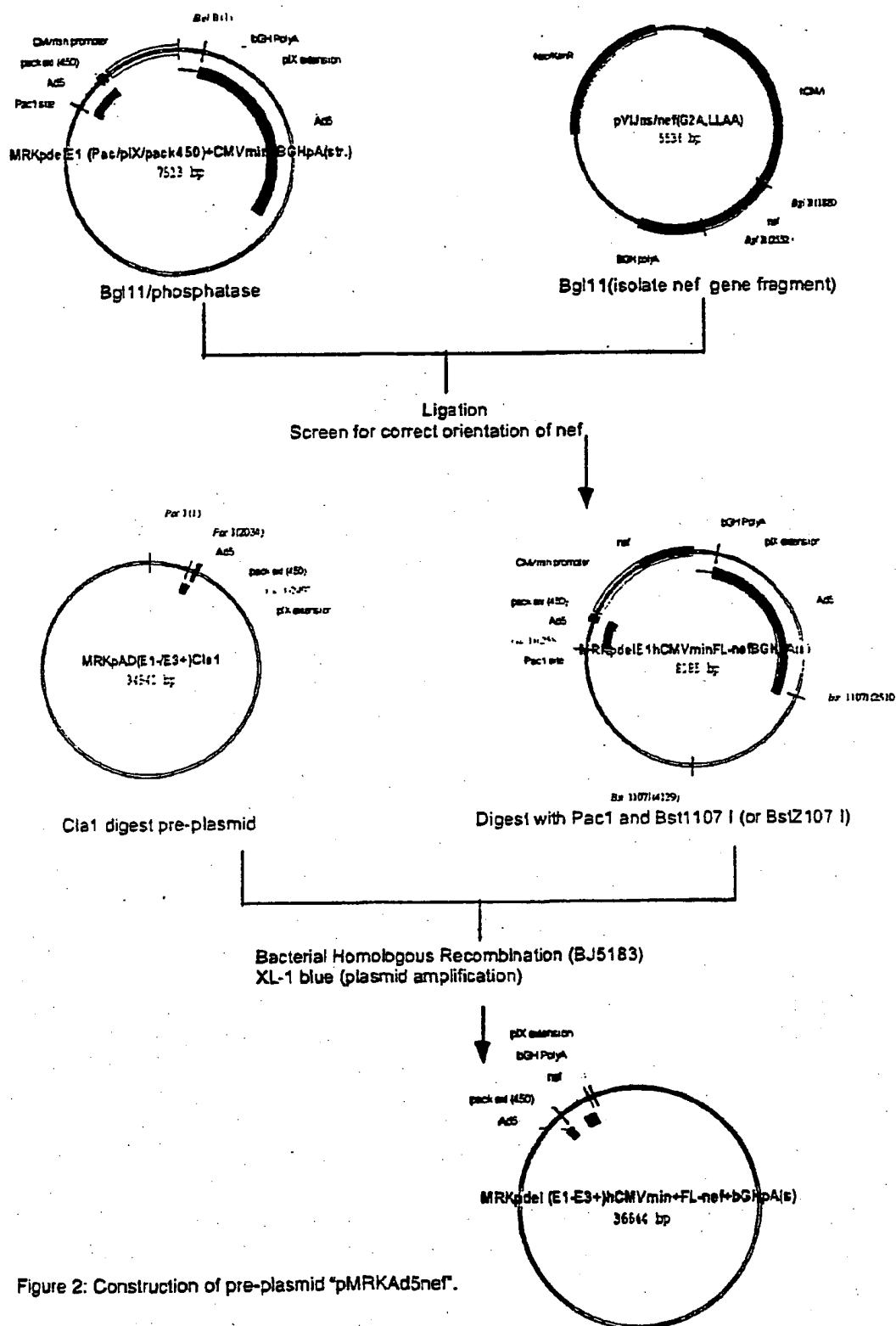
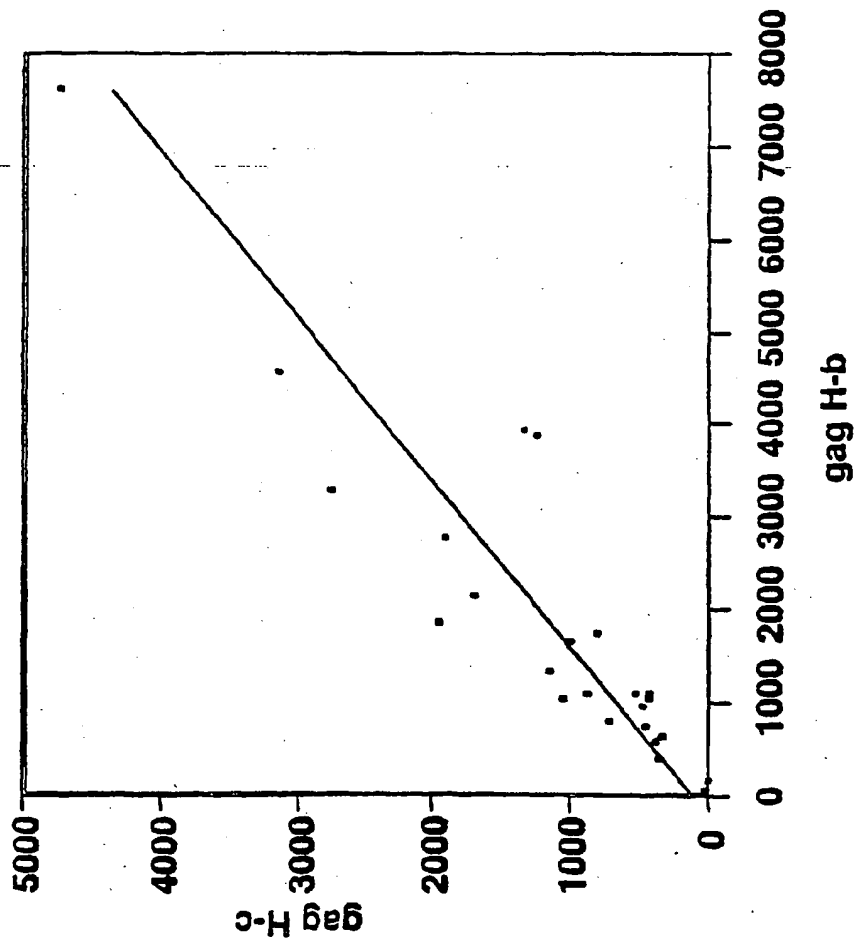


Figure 2: Construction of pre-plasmid "pMRKAd5nef".

FIGURE 23

# Comparison of Clade B vs. Clade C Anti-gag T Cell Responses in Clade B HIV-Infected Subjects



Linear Fit

$$\text{gag H-c} = 111.603 + 0.55866 \text{ gag H-b}$$

Summary of Fit

RSquare	0.816775
RSquare Adj	0.80914
Root Mean Square Error	474.9639
Mean of Response	1158.115
Observations (or Sum Wgts)	26

# Comparison of Clade B vs. Clade C Anti-nef T Cell Responses in Clade B HIV-Infected Subjects

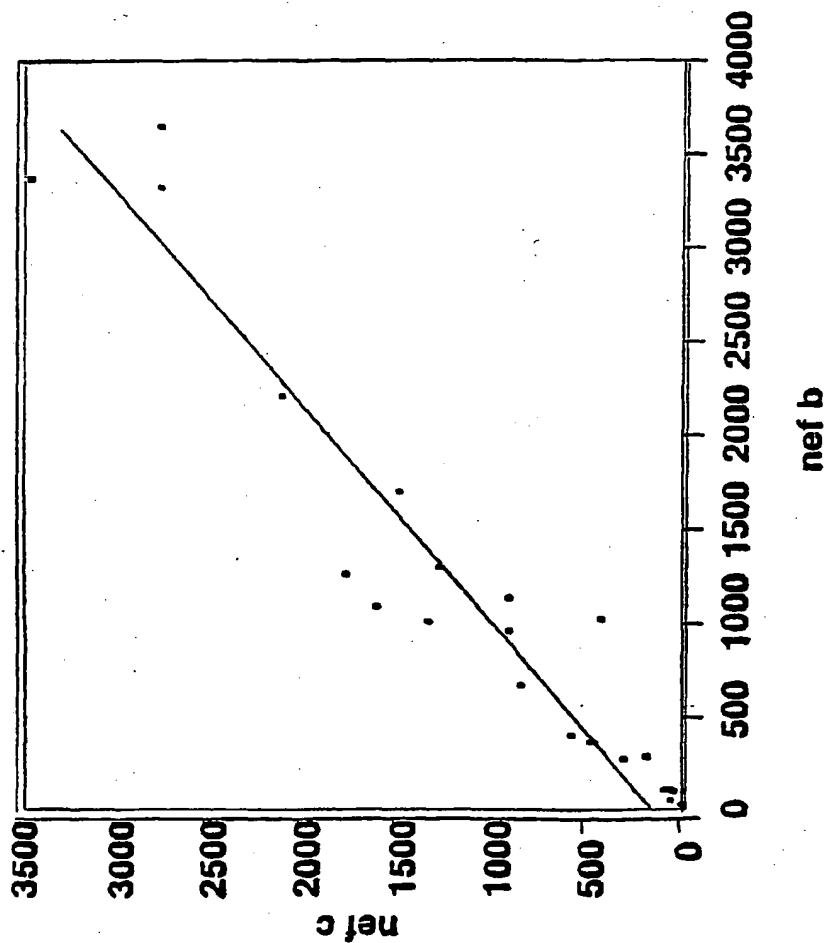


FIGURE 25

Summary of Fit	
RSquare	0.91685
RSquare Adj	0.91289
Root Mean Square Error	289.7718
Mean of Response	1096.435
Observations (or Sum Wgts)	23

**MRKAd5pol MER1062**  
(MRKAd5 Pre-Adenoviral Vector Containing the IA opt pol Coding Region)

```

1  CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG
   GTAGTAGTTA TTATATGGAA TAAACCTAA CTTCGGTTAT ACTATTACTC

51  GGGGTGGAGT TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG
   CCCACCTCA AACACTGCAC CGCGCCCCGC ACCCTTGCCC CGCCCACTGC

101 TAGTAGTGTG GCGGAAGTGT GATGTTGCAA GTGTGGCGGA ACACATGTAA
   ATCATCACAC CGCCTTCACA CTACAACGTT CACACCGCCT TGTGTACATT

151 GCGACGGATG TGGCAAAAGT GACGTTTTTG GTGTGCGCCG GTGTACACAG
   CGCTGCCTAC ACCGTTTCA CTGCAAAAAC CACACGCGGC CACATGTGTC

201 GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG TAAATTGGG
   CTCACTGTT AAAAGCGCGC CAAAATCCGC CTACAACATC ATTTAAACCC

251 CGTAACCGAG TAAGATTGG CCATTTTCGC GGGAAAAC TG AATAAGAGGA
   GCATTGGCTC ATTCTAAACC GGTAAGCG CCCTTTTGAC TTATTCTCCT

301 AGTGAAATCT GAATAATTTT GTGTTACTCA TAGCGCGTAA TATTTGTCTA
   TCACCTTAGA CTTATTAAAA CACAATGAGT ATCGCGCATT ATAAACAGAT

351 GGGCCGCGGG GACTTTGACC GTTTACGTGG AGACTCGCCC AGGTGTTTTT
   CCCGGCGCCC CTGAAACTGG CAAATGCACC TCTGAGCGGG TCCACAAAAA

401 CTCAGGTGTT TTCCGCGTTC CGGGTCAAAG TTGGCGTTTT ATTATTATAG
   GAGTCCACAA AAGGCGCAAG GCCCAGTTTC AACCGCAAAA TAATAATATC

451 GCGGCGCGGA TCCATTGCAT ACGTTGTATC CATATCATAA TATGTACATT
   CGCCGGCGCT AGGTAACGTA TGCAACATAG GTATAGTATT ATACATGTAA

501 TATATTGGCT CATGTCCAAC ATTACGCCCA TGTGACATT GATTATTGAC
   ATATAACCGA GTACAGGTG TAATGGCGGT ACAACTGTAA CTAATAACTG

551 TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA
   ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA TCGGGTATAT

601 TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCCGC TGGCTGACCG
   ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC

651 CCCAACGACC CCCGCCCAT TACGTCAATA ATGACGTATG TTCCCATAGT
   GGGTTGCTGG GGGCGGGTAA CTGCAGTTAT TACTGCATAC AAGGGTATCA

701 AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT
   TTGCGGTTAT CCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

751 AAAGTGGCCA CTGGGAGTA CATCAAGTGT ATCATATGCC AAGTACGCCC
   TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCATGCGGG

801 CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCAGTA
   GGATAACTGC AGTTACTGCC ATTTACGGG CGGACCGTAA TACGGGTCAAT

851 CATGACCTTA TGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA
   GTACTGGAAT ACCCTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT

```

*Figure 26A*

901 TCGCTATTAC GGTGATG CGGTTTGGC AGTACATCAA TGGGCG EA  
AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

951 TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA  
ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT AACTGCAGTT

1001 TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA  
ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

1051 ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG  
TGTTGAGGCG GGGTAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC

1101 GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG  
CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

1151 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC  
GGTAGGTGCG ACAAACCTGG AGGTATCTTC TGTGGCCCTG GCTAGGTCGG

1201 TCCGCGGCGG GGAACGGTGC ATTGGAACGC GGATTCCCCG TGCCAAGAGT  
AGGCGCCGCG CCTTGCCACG TAACCTTGCG CCTAAGGGG ACGGTTCTCA

1251 GAGATCTACC ATGGCCCCCA TCTCCCCAT TGAGACTGTG CCTGTGAAGC  
CTCTAGATGG TACCGGGGGT AGAGGGGGTA ACTCTGACAC GGACACTTCG

1301 TGAAGCCTGG CATGGATGGC CCCAAGGTGA AGCAGTGGCC CCTGACTGAG  
ACTTCGGACC GTACCTACCG GGGTTCCACT TCGTCACCGG GGACTGACTC

1351 GAGAAGATCA AGGCCCTGGT GGAAATCTGC ACTGAGATGG AGAAGGAGGG  
CTCTTCTAGT TCCGGGACCA CCTTTAGACG TGACTCTACC TCTTCTCCCC

1401 CAAAATCTCC AAGATTGGCC CCGAGAACCC CTACAACACC CCTGTGTTTG  
GTTTTAGAGG TTCTAACCGG GGCTCTTGGG GATGTTGTGG GGACACAAAC

1451 CCATCAAGAA GAAGGACTCC ACCAAGTGGA GGAAGCTGGT GGACTTCAGG  
GGTAGTTCTT CTTCCTGAGG TGGTTCACCT CCTTCGACCA CCTGAAGTCC

1501 GAGCTGAACA AGAGGACCCA GGACTTCTGG GAGGTGCAGC TGGGCATCCC  
CTCGACTTGT TCTCCTGGGT CCTGAAGACC CTCCACGTCG ACCCGTAGGG

1551 CCACCCCGCT GGCCTGAAGA AGAAGAGTC TGTGACTGTG CTGGCTGTGG  
GGTGGGGCGA CCGGACTTCT TCTTCTTCAG ACACTGACAC GACCGACACC

1601 GGGATGCCTA CTCTCTGTG CCCCTGGATG AGGACTTCAG GAAGTACACT  
CCCTACGGAT GAAGAGACAC GGGGACCTAC TCCTGAAGTC CTTTATGTGA

1651 GCCTTCACCA TCCCCCTCAT CAACAATGAG ACCCCTGGCA TCAGGTACCA  
CGGAAGTGTT AGGGGAGGTA GTTGTACTC TGGGGACCGT AGTCCATGGT

1701 GTACAATGTG CTGCCCCAGG GCTGGAAGGG CTCCCCTGCC ATCTTCCAGT  
CATGTTACAC GACGGGGTCC CGACCTTCCC GAGGGGACGG TAGAAGGTCA

1751 CCTCCATGAC CAAGATCCTG GAGCCCTTCA GGAAGCAGAA CCCTGACATT  
GGAGGTACTG GTTCTAGGAC CTCGGGAAGT CCTTCGTCTT GGGACTGTAA

1801 GTGATCTACC AGTACATGGC TGCCCTGTAT GTGGGCTCTG ACCTGGAGAT  
CACTAGATGG TCATGTACCG ACGGGACATA CACCCGAGAC TGGACCTCTA

Figure 26B

1851 TGGGCAGCAC ACCAAGA TTGAGGAGCT GAGGCAGCAC CTGCTG T  
ACCCGTCGTG TCCTGGTTCT AACTCCTCGA CTCGTCGTG GACGACTCA

1901 GGGGCCTGAC CACCCCTGAC AAGAAGCACC AGAAGGAGCC CCCCTTCCTG  
CCCCGGACTG GTGGGGACTG TTCTTCGTGG TCTTCCTCGG GGGGAAGGAC

1951 TGGATGGGCT ATGAGCTGCA CCCCACAAAG TGGACTGTGC AGCCCATTTGT  
ACCTACCCGA TACTCGACGT GGGGCTGTTT ACCTGACACG TCGGGTAACA

2001 GCTGCCTGAG AAGGACTCCT GGA CTGTGAA TGACATCCAG AAGCTGGTGG  
CGACGGACTC TTCTGAGGA CCTGACACTT ACTGTAGGTC TTCGACCACC

2051 GCAAGCTGAA CTGGGCCTCC CAAATCTACC CTGGCATCAA GGTGAGGCAG  
CGTTCGACTT GACCCGGAGG GTTTAGATGG GACCGTAGTT CCACTCCGTG

2101 CTGTGCAAGC TGCTGAGGGG CACCAAGGCC CTGACTGAGG TGATCCCCCT  
GACACGTTG ACGACTCCCC GTGGTTCCGG GACTGACTCC ACTAGGGGGA

2151 GACTGAGGAG GCTGAGCTGG AGCTGGCTGA GAACAGGGAG ATCTGAAGG  
CTGACTCCTC CGACTCGACC TCGACCGACT CTTGTCCCTC TAGGACTTCC

2201 AGCCTGTGCA TGGGGTGTA TATGACCCCT CCAAGGACCT GATTGCTGAG  
TCGGACACGT ACCCCACATG ATACTGGGGA GGTTCCTGGA CTAACGACTC

2251 ATCCAGAAGC AGGGCCAGGG CCACTGGACC TACCAAATCT ACCAGGAGCC  
TAGGTCTTCG TCCCGGTCCC GGTACCTGG ATGGTTTAGA TGGTCTCGG

2301 CTTCAAGAAC CTGAAGACTG GCAAGTATGC CAGGATGAGG GGGGCCACA  
GAAGTTCTTG GACTTCTGAC CGTTCATACG GTCTACTCC CCCC GGGTGT

2351 CCAATGATGT GAAGCAGCTG ACTGAGGCTG TGCAGAAGAT CACCACTGAG  
GGTTACTACA CTTGCTGAC TGACTCCGAC ACGTCTTCTA GTGGTGA CT

2401 TCCATTGTGA TCTGGGGCAA GACCCCAAG TTCAAGCTGC CCATCCAGAA  
AGGTAACACT AGACCCCGTT CTGGGGGTC AAGTTCGACG GGTAGGTCTT

2451 GGAGACCTGG GAGACCTGGT GGA CTGAGTA CTGGCAGGCC ACCTGGATCC  
CCTCTGACCT CTCTGGACCA CTTGACTCAT GACCGTCCG TGGACCTAGG

2501 CTGAGTGGGA GTTGTGAAC ACCCCCCCCT TGGTGAAGCT GTGGTACCAG  
GACTCACCTT CAAACACTTG TGGGGGGGG ACCACTTCGA CACCATGGTC

2551 CTGGAGAAGG AGCCCATTTGT GGGGCTGAG ACCTTCTATG TGGCTGGGGC  
GACCTCTTCC TCGGGTAACA CCCC GACTC TGGAGATAC ACCGACCCG

2601 TGCCAACAGG GAGACCAAGC TGGSCAAGGC TGGCTATGTG ACCAACAGGG  
ACGGTTGTCC CTCTGGTTCTG ACCCGTTCCG ACCGATACAC TGGTTGTCCC

2651 GCAGGCAGAA GGTGGTGACC CTGACTGACA CCACCAACCA GAAGACTGCC  
CGTCCGTCTT CCACCACTGG GACTGACTGT GGTGGTTGGT CTTCTGACGG

2701 CTCCAGGCCA TCTACCTGGC CCTCCAGGAC TCTGGCCTGG AGGTGAACAT  
GAGGTCCGGT AGATGGACCG GGAGGTCTTG AGACCGGACC TCCACTTGTA

2751 TGTGACTGCC TCCAGTATG CCCTGGGCAT CATCCAGGCC CAGCCTGATC  
ACACTGACGG AGGGTCATAC GGGACCCGTA GTAGGTCCGG GTCGSACTAG

Figure 26C

2801 AGTCTGAGTC TCTGGTG AACCAGATCA TTGAGCAGCT GATCAA G  
 TCAGACTCAG ACTCGACCAC TTGGTCTAGT AACTCGTCGA CTAGTCTTC  
 2851 GAGAAGGTGT ACCTGGCCTG GGTGCCTGCC CACAAGGGCA TTGGGGGCAA  
 CTCTTCCACA TGGACCGGAC CCACGGACGG GTGTTCCCGT AACCCCGTT  
 2901 TGAGCAGGTG GACAAGCTGG TGTCTGCTGG CATCAGGAAG GTGCTGTTCC  
 ACTCGTCCAC CTGTTGACAC ACAGACGACC GTAGTCCTTC CACGACAAGG  
 2951 TGGATGGCAT TGACAAGGCC CAGGATGAGC ATGAGAAGTA CCACTCCAAC  
 ACCTACCGTA ACTGTTCCGG GTCCTACTCG TACTCTTCAT GGTGAGGTTG  
 3001 TGGAGGGCTA TGGCCTCTGA CTTCAACCTG CCCCCTGTGG TGGCTAAGGA  
 ACCTCCCGAT ACCGGAGACT GAAGTTGGAC GGGGGACACC ACCGATTCTT  
 3051 GATTGTGGCC TCCTGTGACA AGTGCCAGCT GAAGGGGGAG GCCATGCATG  
 CTAACACCGG AGGACACTGT TCACGGTCGA CTCCCCCTC CGGTACGTAC  
 3101 GGCAGGTGGA CTGCTCCCTT GGCATCTGGC AGCTGGCCTG CACCCACCTG  
 CCGTCCACCT GACGAGGGGA CCGTAGACCG TCGACCGGAC GTGGGTGGAC  
 3151 GAGGGCAAGG TGATCCTGGT GGCTGTGCAT GTGGCCTCCG GCTACATTGA  
 CTCCCGTTCC ACTAGGACCA CCGACACGTA CACCGGAGGC CGATGTAAC  
 3201 GGCTGAGGTG ATCCCTGCTG AGACAGGCCA GGAGACTGCC TACTTCCTGC  
 CCGACTCCAC TAGGGACGAC TCTGTCCGGT CCTCTGACGG ATGAAGGACG  
 3251 TGAAGCTGGC TGGCAGGTGG CCTGTGAAGA CCATCCACAC TGCCAATGGC  
 ACTTCGACCG ACCGTCCACC GGACACTTCT GGTAGGTGTG ACGGTTACCG  
 3301 TCCAACCTCA CTGGGGCCAC AGTGAGGGCT GCCTGCTGGT GGGCTGGCAT  
 AGGTTGAAGT GACCCCGGTG TCACTCCCGA CGGACGACCA CCCGACCGTA  
 3351 CAAGCAGGAG TTTGGCATCC CCTACAACCC CCAGTCCCAG GGGGTGGTGG  
 GTTCGTCTC AAACCGTAGG GGATGTTGGG GGTGAGGGTC CCCCACCACC  
 3401 CCTCCATGAA CAAGGAGCTG AAGAAGATCA TTGGGCAGGT GAGGGACCAG  
 GGAGGTACTT GTTCCTCGAC TTCTTCTAGT AATCCGTCCA CTCCTGGTC  
 3451 GCTGAGCACC TGAAGACAGC TGTGCAGATG GCTGTGTTCA TCCACAACCT  
 CGACTCGTGG ACTTCTGTG ACACGTCTAC CGACACAAGT AGGTGTTGAA  
 3501 CAAGAGGAAG GGGGGCATCG GGGGCTACTC CGCTGGGGAG AGGATTGTGG  
 GTTCTCCTTC CCCCCGTAGC CCCCATGAG GCGACCCCTC TCCTAACACC  
 3551 ACATCATTCG CACAGACATC CAGACCAAGG AGCTCCAGAA GCAGATCACC  
 TGTAGTAACG GTGTCTGTAG GTCTGGTTCC TCGAGGTCTT CGTCTAGTGG  
 3601 AAGATCCAGA ACTTCAGGST GTACTACAGG GACTCCAGGA ACCCCCTGTG  
 TTCTAGGTCT TGAAGTCCCA CATGATGTCC CTGAGGTCTT TGGGGGACAC  
 3651 GAAGGGCCCT GCCAAGCTGC TGTGGAAGGG GGAGGGGGCT GTGGTGATCC  
 CTTCCCGGGA CGGTTGACG ACACCTTCCC CCTCCCCGA CACCACTAGG  
 3701 AGGACAATCT TGACATCAAG GTGGTGCCCA GGAGGAAGGC CAAGATCATC  
 TCCTGTTGAG ACTGTAGTTC CACCACGGGT CCTCCTTCCG GTTCTAGTAG

Figure 26 D

3751 AGGGACTATG GAGCAGAT GGCTGGGGAT GACTGTGTGG CCTCCATCA  
TCCTTGATAC CATTGCTCTA CCGACCCCTA CTGACACACC GGAGGTGGT

3801 GGATGAGGAC TAAAGCCCGG GCAGATCTGC TGTGCCTTCT AGTTGCCAGC  
CCTACTCCTG ATTTCCGGGC CGTCTAGACG ACACGGAAGA TCAACGGTCG

3851 CATCTGTTGT TTGCCCCCTC CCCGTGCCTT CCTTGACCCT GGAAGGTGCC  
GTAGACAACA AACGGGGAGG GGGCACGGAA GGAAC TGGA CCTTCCACGG

3901 ACTCCCACTG TCCTTTCCCTA ATAAAATGAG GAAATGTCAT CGCATTGTCT  
TGAGGGGTGAC AGGAAAGGAT TATTTTACTC CTTTAACGTA GCGTAACAGA

3951 GAGTAGGTGT CATCTATTTC TGGGGGGTGG GGTGGGGCAG GACAGCAAGG  
CTCATCCACA GTAAGATAAG ACCCCCCACC CCACCCCGTC CTGTCGTTCC

4001 GGGAGGATTG GGAAGACAAT AGCAGGCATG CTGGGGATGC GGTGGGCTCT  
CCCTCCTAAC CCTTCTGTTA TCGTCCGTAC GACCCCTACG CCACCCGAGA

4051 ATGGCCGATC GGC GCGCCGT ACTGAAATGT GTGGGCGTGG CTTAAGGGTG  
TACCGGCTAG CCGCGCGCA TGACTTTACA CACCCGCACC GAATTTCCAC

4101 GGAAAGAATA TATAAGGTGG GGGTCTTATG TAGTTTTGTA TCTGTTTTGC  
CCTTTCTTAT ATATTCCACC CCCAGAATAC ATCAAAACAT AGACAAAACG

4151 AGCAGCCGCC GCCGCCATGA GCACCAACTC GTTTGATGGA AGCATTGTGA  
TCGTCGGCGG CCGCGGTACT CGTGGTTGAG CAAACTACCT TCGTAACACT

4201 GCTCATATTT GACAACGCGC ATGCCCCCAT GGGCCGGGGT GCGTCAGAAT  
CGAGTATAAA CTGTTGCGCG TACGGGGGTA CCCGGCCCCA CGCAGTCTTA

4251 GTGATGGGCT CCAGCATTGA TGGTCGCCCC GTCCTGCCCC CAAACTCTAC  
CACTACCCGA GGTGCTAACT ACCAGCGGGG CAGGACGGGC GTTTGAGATG

4301 TACCTTGACC TACGAGACCG TGTCTGGAAC GCCGTGGAG ACTGCAGCCT  
ATGGAACCTG ATGCTCTGGC ACAGACCTTG CGGCAACCTC TGACGTCGGA

4351 CCGCCGCCGC TTCAGCCGCT GCAGCCACCG CCCGCGGGAT TGTGACTGAC  
GGCGCGGGCG AAGTCGGCGA CGTCGCTGGC GGGCGCCCTA AACTGACTG

4401 TTTGCTTTCC TGAGCCCGCT TGCAACAGT GCAGCTTCCC GTTCATCCGC  
AAACGAAAGG ACTCGGGCGA ACGTTGTCA CGTCGAAGGG CAAGTAGGCG

4451 CCGCGATGAC AAGTTGACGG CTCTTTTGGC ACAATTGGAT TCTTTGACCC  
GGCGCTACTG TTCAACTGCC GAGAAAACCG TGTAAACCTA AGAAACTGGG

4501 GGGAACTTAA TGTGCTTCT CAGCAGCTGT TGGATCTGCC CCAGCAGGTT  
CCCTTGAATT ACAGCAAAGA GTCGTCGACA ACCTAGACGC GGTCTGTCAA

4551 TCTGCCCTGA AGGCTTCCTC CCCTCCCAAT GCGGTTTAA ACATAAATAA  
AGACGGGACT TCCGAAGGAG GGGAGGGTTA CGCCAAATTT TGTATTTATT

4601 AAAACCAGAC TCTGTTTGA TTTGGATCAA GCAAGTGTCT TGCTGTCTTT  
TTTGGTCTG AGACAAACCT AAACCTAGTT CGTTCACAGA ACGACAGAAA

4651 ATTTAGGGGT TTTGCGCGCG CGGTAGGCCC GGGACCAGCG GTCTCGGTCG  
TAAATCCCCA AAACGCGCGC GCCATCCGGG CCCTGGTCGC CAGAGCCAGC

Figure 26E

4701 TTGAGGGTCC TGTGTATTTT TTCCAGGACG TGGTAAAGGT-GACTCTGAT  
 AACTCCCAGG AATAAAA AAGGTCTTC ACCATTTCCA CTGAGA A  
 4751 GTTCAGATAC ATGGGCATAA GCCCGTCTCT GGGGTGGAGG TAGCACCAC  
 CAAGTCTATG TACCCGTATT CGGGCAGAGA CCCACCTCC ATCGTGGTGA  
 4801 GCAGAGCTTC ATGCTGCGGG GTGGTGTGT AGATGATCCA GTCGTAGCAG  
 CGTCTCGAAG TACGACGCCC CACCACAACA TCTACTAGGT CAGCATCGTC  
 4851 GAGCGCTGGG CGTGGTGCCT AAAAATGTCT TTCAGTAGCA AGCTGATTGC  
 CTCGCGACCC GCACCACGGA TTTTACAGA AAGTCATCGT TCGACTAACG  
 4901 CAGGGGCGAG CCCTTGGTGT AAGTGTTTAC AAAGCGGTTA AGCTGGGATG  
 GTCCCCGTCC GGAACCCACA TTCACAAATG TTTCGCCAAT TCGACCCTAC  
 4951 GGTGCATACG TGGGGATATG AGATGCATCT TGGACTGTAT TTTTAGGTTG  
 CCACGTATGC ACCCCTATAC TCTACGTAGA ACCTGACATA AAAATCCAAC  
 5001 GCTATGTTCC CAGCCATATC CCTCCGGGGA TTCATGTTGT GCAGAACCAC  
 CGATACAAGG GTCGGTATAG GGAGGCCCT AAGTACAACA CGTCTTGGTG  
 5051 CAGCACAGTG TATCCGGTGC ACTTGGGAAA TTTGTCTATG AGCTTAGAAG  
 GTCGTGTAC ATAGGCCACG TGAACCCCTT AACAGTACA TCGAATCTTC  
 5101 GAAATGCGTG GAAGAACTTG GAGACGCCCT TGTGACCTCC AAGATTTTCC  
 CTTTACGCAC CTTCTTGAAC CTCTCGGGA AACTGGAGG TTCTAAAAGG  
 5151 ATGCATTCGT CCATAATGAT GGCAATGGGC CCACGGGCGG CGGCTGGGC  
 TACGTAAGCA GGTATTACTA CCGTTACCG GGTGCCCCG GCCGGACCCG  
 5201 GAAGATATTT CTGGGATCAC TAACGTCATA GTTGTGTTCC AGGATGAGAT  
 CTTCTATAAA GACCCTAGTG ATTGCAGTAT CAACACAAGS TCCTACTCTA  
 5251 CGTCATAGGC CATTTTACA AAGCGCGGGC GGAGGGTGCC AGACTGCGGT  
 GCAGTATCCG GTAAAAATGT TTCGCGCCCG CCTCCACG TCTGACGCCA  
 5301 ATAATGGTTC CATCCGGCCC AGGGGCGTAG TTACCCTCAC AGATTTCAT  
 TATTACCAAG GTAGGCCGGG TCCCCGCATC AATGGGAGTG TCTAAACGTA  
 5351 TTCCCACGCT TTGAGTTCAG ATGGGGGGAT CATGTCTACC TGGGGGGCGA  
 AAGGGTGCGA AACTCAAGTC TACCCCTTA GTACAGATGG ACGCCCGCT  
 5401 TGAAGAAAAC GGTTCGCGG GTAGGGGAGA TCAGCTGGGA AGAAAGCAGG  
 ACTTCTTTTG CCAAAGGCC CATCCCTCT AGTCGACCCT TCTTTCGTCC  
 5451 TTCCTGAGCA GCTGCGACTT ACCGCAGCG GTGGGCGGT AAATCACACC  
 AAGGACTCGT CGACGCTGAA TGGCGTCGGC CACCCGGGCA TTTAGTGTGG  
 5501 TATTACCGGC TGCAACTGGT AGTTAAGAGA GCTGCAGCTG CCGTCATCCC  
 ATAATGGCCG ACGTTGACCA TCAATTCTCT CGACGTCGAC GGCAGTAGGG  
 5551 TGAGCAGGGG GGCCACTTCG TTAAGCATGT CCTGACTCG CATGTTTTCC  
 ACTCGTCCCC CCGGTGAAGC AATTCGTACA GGGACTGAGC GTACAAAAGG  
 5601 CTGACCAAAT CCGCCAGAAG GCGCTCGCG CCCAGCGATA GCAGTTCTTG  
 GACTGTTTA GCGGTCTTC CCGAGCGGC GGTGCTAT CGTCAAGAAC

Figure 26 F

5651 CAAGGAAGCA AATTTTCA ACGTTTGAG ACCGTCCGCC GTAGGCATC  
 GTTCCTTCGT TTCAAAAAGT TGCCAAACTC TGGCAGGCGG CATCCGTACG

5701 TTTTGAGCGT TTGACCAAGC AGTTCCAGGC GGTCCACAG CTCGGTCACC  
 AAAACTCGCA AACTGGTTCG TCAAGGTCCG CCAGGGTGTC GAGCCAGTGG

5751 TGCTCTACGG CATCTCGATC CAGCATATCT CCTCGTTTCG CGGGTTGGGG  
 ACGAGATGCC GTAGAGCTAG GTCGTATAGA GGAGCAAAGC GCCCAACCCC

5801 CGGCTTTTCG TGTACGGCAG TAGTCGGTGC TCGTCCAGAC GGGCCAGGGT  
 GCCGAAAGCG ACATGCCGTC ATCAGCCACG AGCAGGTCTG CCCGGTCCCA

5851 CATGTCTTTC CACGGGCGCA GGGTCTCTGT CAGCGTAGTC TGGGTCACGG  
 GTACAGAAAG GTGCCCCGCT CCCAGGAGCA GTCGCATCAG ACCCAGTGCC

5901 TGAAGGGGTG CGCTCCGGGC TGCGCGCTGG CCAGGGTGCG CTTGAGGCTG  
 ACTTCCCCAC GCGAGGCCCG ACGCGCGACC GGTCCCACGC GAACTCCGAC

5951 GTCTCTGCTG TGCTGAAGCG CTGCCGGTCT TCGCCCTGCG CGTCGGCCAG  
 CAGGACGACC ACGACTTTCG GACGGCCAGA AGCGGGACGC GCAGCCGGTC

6001 GTAGCATTTG ACCATGGTGT CATAGTCCAG CCCCTCCGCG GCGTGCCCT  
 CATCGTAAAC TGGTACCACA GTATCAGGTC GGGGAGGCGC CGCACCGGGA

6051 TGGCGCGCAG CTTGCCCTTG GAGGAGGCGC CGCACGAGGG GCAGTCAGA  
 ACCGCGCGTC GAACGGGAAC CTCTCCGCG GCGTGCTCCC CGTCACGTCT

6101 CTTTTGAGGG CGTAGAGCTT GGGCGCGAGA AATACCGATT CCGGGGAGTA  
 GAAAACCTCC GCATCTCGAA CCCGCGCTCT TTATGGCTAA GGCCCTCAT

6151 GGCATCCGCG CCGCAGGCCC CGCAGACGGT CTCGCATTCC ACGAGCCAGG  
 CCGTAGGCGC GCGCTCCGGG GCGTCTGCCA GAGCGTAAGG TGCTCGGTCC

6201 TGAGCTCTGG CCGTTCGGGG TCAAAAACCA GGTTCCCCC ATGCTTTTTG  
 ACTCGAGACC GGCAAGCCCC AGTTTTTGGT CCAAAGGGGG TACGAAAAAC

6251 ATGCGTTTCT TACCTCTGGT TTCCATGAGC CGGTGTCCAC GCTCGGTGAC  
 TACGCAAGA ATGGAGACCA AAGGTACTCG GCCACAGGTG CGAGCCACTG

6301 GAAAAGGCTG TCCGTGTCCC CGTATACAGA CTTGAGAGGC CTGTCTCGA  
 CTTTTCGAC AGGCACAGGG GCATATGTCT GAACTCTCCG GACAGGAGCT

6351 GCGGTGTTCC GCGTCTCTCC TCGTATAGAA ACTCGGACCA CTCTGAGACA  
 CGCCACAAGG CGCCAGGAGG AGCATATCTT TGAGCCTGGT GAGACTCTGT

6401 AAGGCTCGCG TCCAGGCCAG CACGAAGGAG GCTAAGTGGG AGGGGTAGCG  
 TTCCGAGCGC AGGTCCGGTC GTGCTTCCTC CGATTCAACC TCCCACATCGC

6451 GTCGTTGTCC ACTAGGGGGT CCACTCGCTC CAGGGTGTGA AGACACATGT  
 CAGCAACAGG TGATCCCCCA GGTGAGCGAG GTCCCACT TCTGTGTACA

6501 CGCCCTCTTC GGCATCAAGG AAGGTGATTG GTTTGTAGGT GTAGGCCACG  
 GCGGGAGAAG CCGTAGTTCC TTCCACTAAC CAAACATCCA CATCCGGTGC

6551 TGACCGGGTG TTCCTGAAGG GGGGCTATAA AAGGGGTGG GGGCGCGTTC  
 ACTGGCCAC AAGGACTTCC CCCGATATT TTCCCCACC CCCGCGCAAG

Figure 266

6601 GTCCTCACTC TCTTCCGCAT CGCTGTCTGC GAGGGCCATC TGTGCTGCTG  
 CAGGAGTGAG AGGCGTA GCGACAGACG CTCCCGGTCTG ACAACGAC  
 6651 AGTACTCCCT CTGAAAAGCG GGCATGACTT CTGCGCTAAG ATTGTCACTT  
 TCATGAGGGA GACTTTTCGC CCGTACTGAA GACGCGATTG TAACAGTCAA  
 6701 TCCAAAAACG AGGAGGATTT GATATTCACC TGGCCCCGCG TGATGCCTTT  
 AGGTTTTTGC TCCTCCTAAA CTATAAGTGG ACCGGGCGCC ACTACGGA  
 6751 GAGGGTGGCC GCATCCATCT GGTGAGAAAA GACAATCTTT TTGTTGTCAA  
 CTCCCACCGG CGTAGGTAGA CCAGTCTTTT CTGTTAGAAA AACAACAGTT  
 6801 GCTTGGTGGC AAACGACCCG TAGAGGGCGT TGGACAGCAA CTTGGCGATG  
 CGAACCACCG TTTGCTGGGC ATCTCCCGCA ACCTGTCTGT GAACCGCTAC  
 6851 GAGCGCAGGG TTTGGTTTTT GTCGCGATCG GCGCGCTCCT TGGCCGCGAT  
 CTCGCGTCCC AAACCAAAA CAGCGCTAGC CGCGCGAGGA ACCGGCGCTA  
 6901 GTTAGCTGC ACGTATTCGC GCGCAACGCA CCGCCATTCT GGAAAGACGG  
 CAAATCGACG TGCATAAGCG CGCGTTGCGT GCGGTAAGC CCTTCTGCCC  
 6951 TGGTGCCTC GTCGGGCACC AGGTGCACGC GCCAACCGCG GTTGTGCAGG  
 ACCACGCGAG CAGCCCGTGG TCCACGTGCG CGGTGGCGC CAACACGTCC  
 7001 GTGACAAGGT CAACGCTGGT GGCTACCTCT CCGCGTAGGC GCTCGTGGT  
 CACTGTTCCA GTTGCACCA CCGATGGAGA GGCGCATCCG CGAGCAACCA  
 7051 CCAGCAGAGG CGGCGGCCCT TGCGCGAGCA GAATGGCGGT AGGGGGTCTA  
 GGTGCTCTCC GCGCGCGGA ACGCGCTCGT CTTACCGCA TCCCCAGAT  
 7101 GCTGCGTCTC GTCCGGGGG TCTGCGTCCA CGGTAAAGAC CCCGGGAGC  
 CGACGCAGAG CAGGCCCCC AGACGCAGGT GCCATTCTG GGGCCCGTCTG  
 7151 AGGCGCGCGT CGAAGTAGTC TATCTTGCAT CCTTGCAAGT CTAGCGCCTG  
 TCCGCGCGCA GCTTCATCAG ATAGAACGTA GGAACGTCA GATCGCGGAC  
 7201 CTGCCATGCG CGGGCGGCAA GCGCGCGCTC GTATGGGTTG AGTGGGGGAC  
 GACGGTACGC GCCCGCCGTT CGCGCGGAG CATACCCAAC TCACCCCTG  
 7251 CCCATGGCAT GGGGTGGGTG AGCGCGGAGG CGTACATGCC GCAAATGTCTG  
 GGGTACCGTA CCCACCCAC TCGCGCTCTC GCATGTACGG CGTTTACAGC  
 7301 TAAACGTAGA GGGGCTCTCT GAGTATTCCA AGATATGTAG GGTAGCATCT  
 ATTTGCATCT CCCCAGAGA CTCATAAGGT TCTATACATC CCATCGTAGA  
 7351 TCCACCGCGG ATGCTGGCGC GCACGTAATC GTATAGTTCTG TCGAGGGAG  
 AGGTGGCGCC TACGACCGCG CGTGCATTAG CATATCAAGC ACGCTCCCTC  
 7401 CGAGGAGGTC GGGACCGAGG TTGCTACGGG CGGGCTGCTC TGCTCGGAAG  
 GCTCCTCCAG CCTTGCTCC AACGATGCCC GCGCGAGAG ACGAGCCTTC  
 7451 ACTATCTGCC TGAAGATGGC ATGTGAGTTG GATGATATGG TTGGACGCTG  
 TGATAGACGG ACTTCTACCG TACACTCAAC CTACTATACC AACCTGCGAC  
 7501 GAAGACGTTG AAGCTGGCGT CTGTGAGACC TACCGCGTCA CGCACGAAGG  
 CTTCTGCAAC TTCGACCGCA GACACTCTGG ATGGCGCAGT GCGTGCTTCC

Figure 26 H

7551 AGGCGTAGGA GCGCAGC TTGTTGACCA GCTCGGCGGT GACCTG G  
TCCGCATCCT CAGCGCGTCG AACAACTGGT CGAGCCGCCA CTGGACGTGC

7601 TCTAGGGCGC AGTAGTCCAG GGTTCCTTG ATGATGTCAT ACTTATCCTG  
AGATCCCGCG TCATCAGGTC CCAAAGGAAC TACTACAGTA TGAATAGGAC

7651 TCCCTTTTTT TTCCACAGCT CGCGGTTGAG GACAACTCT TCGCGGTCTT  
AGGGAAAAAA AAGGTGTCGA GCGCCAACTC CTGTTTGAGA AGCGCCAGAA

7701 TCCAGTACTC TTGGATCGGA AACCCGTCGG CCTCCGAACG GTAAGAGCCT  
AGGTCATGAG AACCTAGCCT TTGGGCAGCC GGAGGCTTGC CATTCTCGGA

7751 AGCATGTAGA ACTGGTTGAC GGCCTGGTAG GCGCAGCATC CCTTTTCTAC  
TCGTACATCT TGACCAACTG CCGGACCATC CGCGTCGTAG GGAAGATG

7801 GGGTAGCGCG TATGCCCTGCG CGGCCCTCCG GACCGAGGTG TGGGTGAGCG  
CCCATCGCGC ATACGGGACGC GCCGGAAGGC CTCGCTCCAC ACCCACTCGC

7851 CAAAGGTGTC CCTGACCATG ACTTTGAGGT ACTGGTATTT GAAGTCAGTG  
GTTTCCACAG GGACTGGTAC TGAACTCCA TGACCATAAA CTTCACTCAC

7901 TCGTCGCATC CGCCCTGCTC CCAGAGCAAA AAGTCCGTGC GCTTTTGGGA  
AGCAGCGTAG GCGGGACGAG GGTCTCGTTT TTCAGGCACG CGAAAAACCT

7951 ACGCGGATTT GCGAGGGCGA AGGTGACATC GTTGAAGAGT ATCTTTCCCG  
TGCGCTTAAA CCGTCCCGCT TCCACTGTAG CAACTTCTCA TAGAAAGGGC

8001 CGCGAGGCAT AAAGTTGCGT GTGATGCGGA AGGGTCCCGG CACCTCGGAA  
GCGCTCCGTA TTCAACGCA CACTACGCCT TCCAGGGCC GTGGAGCCTT

8051 CGGTGTTAA TTACCTGGGC GCGGAGCACG ATCTCGTCAA AGCCGTTGAT  
GCCAACAAAT AATGGACCCG CCGCTCGTGC TAGAGCAGTT TCGGCAACTA

8101 GTTGTGGCCC ACAATGTAAA GTTCCAAGAA GCGCGGGATG CCCTTGATGG  
CAACACCGGG TGTTACATTT CAAGGTTCTT CCGCCCTTAC GGGAACTACC

8151 AAGGCAATTT TTTAAGTTCC TCGTAGGTEA GCTCTTCAGG GGAGCTGAGC  
TTCCGTTAAA AAATTCAAGG AGCATCCACT CGAGAAGTCC CCTCGACTCG

8201 CCGTGCTCTG AAAGGGCCCA GTCTGCAAGA TGAGGGTTGG AAGCGACGAA  
GGCACGAGAC TTTCCCGGGT CAGACGTTCT ACTCCCAACC TTCGCTGCTT

8251 TGAGCTCCAC AGGTACGGG CCATTAGCAT TTGCAGGTGG TCGCGAAAGG  
ACTCGAGGTG TCCAGTGCCC GGTAAATCGTA AACGTCCACC AGCGCTTTCC

8301 TCCTAAACTG GCGACCTATG GCCATTTTTT CTGGGGTGAT GCAGTAGAAG  
AGGATTTGAC CGCTGGATAC CGGTAAAAAA GACCCCACTA CGTCATCTTC

8351 GTAAGCGGGT CTTGTTCCCA GCGGTCCCAT CCAAGGTTCC CGGCTAGGTC  
CATTGCCCCA GAACAAGGGT CGCCAGGTA GGTCCAAGC GCCGATCCAG

8401 TCGCGCGGCA GTCCTAGAG GCTCATCTCC GCCGAACCTC ATGACCAGCA  
AGCGCCCGGT CAGTGATCTC CGAGTAGAGG CGGCTTGAAG TACTGGTCGT

8451 TGAAGGGCAC GAGCTGCTTC CCAAAGGCCC CCATCCAAGT ATAGGTCTCT  
ACTTCCCGTG CTCGACGAAG GGTTCGCGG GGTAGGTTCA TATCCAGAGA

Figure 26I

8501 ACATCGTAGG TAAAGAG ACGCTCGGTG CGAGGATGCG AGCCGA G  
 TGTAGCATCC ACTGTTTCTC TGCAGGCCAC GCTCCTACGC TCGGCTAGCC  
 8551 GAAGAAGTGG ATCTCCCGCC ACCAATTGGA GGAGTGGCTA TTGATGTGGT  
 CTTCTTGACC TAGAGGGCGG TGTTAACCT CCTCACCAGT AACTACACCA  
 8601 GAAAGTAGAA GTCCCTGCGA CGGGCCGAAC ACTCGTGCTG GCTTTTGTA  
 CTTTCATCTT CAGGGACGCT GCCCGCTTG TGAGCACGAC CGAAAACATT  
 8651 AAACGTGCGC AGTACTGGCA GCGGTGCACG GGCTGTACAT CCTGCACGAG  
 TTTGCACGCG TCATGACCGT CGCCACGTGC CCGACATGTA GGACGTGCTC  
 8701 GTTGACCTGA CGACCGCGCA CAAGGAAGCA GAGTGGGAAT TTGAGCCCTT  
 CAACTGGAAT GCTGGCGCGT GTTCCTTCGT CTCACCTTA AACTCGGGGA  
 8751 CGCCTGGCGG GTTGGCTGG TGCTTCTTA CTTGGGCTGC TTGTCCTTGA  
 GCGGACCGCC CAAACCGACC ACCAGAAGAT GAAGCCGACG AACAGGAAT  
 8801 CCGTCTGGCT GCTCGAGGGG AGTTACGGTG GATCGGACCA CCACGCCGCG  
 GGCAGACCGA CGAGCTCCCC TCAATGCCAC CTAGCCTGGT GGTGCGGCGC  
 8851 CGAGCCCAA GTCCAGATGT CCGCGCGCGG CGGTGCGAGC TTGATGACAA  
 GCTCGGGTTT CAGGTCTACA GCGCGCGGCC GCCAGCCTCG AACTACTGTT  
 8901 CATCGCGCAG ATGGGAGCTG TCCATGGTCT GGAGCTCCCG CGGCGTCAGG  
 GTAGCGCGTC TACCCTCGAC AGGTACCAGA CCTCGAGGGC GCCGCAGTCC  
 8951 TCAGGCGGGA GCTCCTGCAG GTTTACCTCG CATAGACGGG TCAGGGCGCG  
 AGTCCGCCCT CGAGGACGTC CAAATGGAGC GTATCTGCC AGTCCGCGC  
 9001 GGCTAGATCC AGGTGATACC TAATTTCCAG GGGCTGGTTG GTGGCGCGCT  
 CCGATCTAGG TCCACTATGG ATTAAAGGTC CCCGACCAAC CACCGCCGCA  
 9051 CGATGGCTTG CAAGAGGCGG CATCCCCGCG GCGCGACTAC GGTACCGCGC  
 GCTACCGAAC GTTCTCCGGC GTAGGGGCGC CGCGCTGATG CCATGGCGCG  
 9101 GGGGGCGGCT GGGCGCGGGG GGTCTCTTG GATGATGCAT CTAAAAGCGG  
 CCGCCCGCA CCGGCGGCC CCACAGGAAC CTACTACGTA GATTTTCGCC  
 9151 TGACGCGGGC GAGCCCCCGG AGGTAGGGG GGCTCCGGAC CCGCCGGGAG  
 ACTGCGCCCG CTCGGGGGCC TCCATCCCC CCGAGGCCTG GCGGCGCCTC  
 9201 AGGGGGCAGG GGCACGTGCG CGCCGCGCGC GGGCAGGAGC TGGTGCTGCG  
 TCCCCCGTCC CCGTGCAGCC GCGGCGCGCG CCCGTCTCG ACCACGACGC  
 9251 CGCGTAGGTT GCTGGCGAAC GCGACGACGC GCGGTTGAT CTCCTGAATC  
 GCGCATCCAA CGACCGCTTG CGCTGCTGCG CCGCCAATA GAGGACTTAG  
 9301 TGGCGCCTCT GCGTGAAGAC GACGGGCCCC GTGAGCTTGA ACCTGAAAGA  
 ACCGCGGAGA CGCACTTCTG CTGCCCCGGC CACTCGAAT TGGACTTTCT  
 9351 GAGTTCGACA GAATCAATT CGGTGTCGTT GACGCGGGCC TGGCGAAAA  
 CTCAGCTGT CTTAGTTAAA GCCACAGCAA CTGCGCGCGG ACCGCGTTTT  
 9401 TCTCTGCAC GTCTCTGAG TTGTCTTGAT AGGCGATCTC GGCCATGAAC  
 AGAGGACGTG CAGAGGACTC AACAGAACTA TCCGCTAGAG CCGGTACTTG

Figure 26 J

9451 TGCTCGATCT C CTCCTG GAGATCTCCG CGTCCGGCTC GCTCCA T  
 ACCAGCTAGA GAAGGAGGAC CTCTAGAGGC GCAGGCCGAG CGAGGTGCCA  
 9501 GCGCGCGAGG TCGTTGGAAA TCGGGGCCAT GAGCTGCGAG AAGGCGTTGA  
 CCGCCGCTCC AGCAACCTTT ACGCCCGGTA CTCGACGCTC TTCCGCAACT  
 9551 GGCCTCCCTC GTTCCAGACG CGGCTGTAGA CCACGCCCCC TTCGGCATCG  
 CCGGAGGGAG CAAGGTCTGC GCCGACATCT GGTGCGGGG AAGCCGTAGC  
 9601 CCGGCGCGCA TGACCACCTG CCGGAGATTG AGCTCCACGT GCCGGGCGAA  
 GCCCGCGCGT ACTGGTGGAC GCGCTCTAAC TCGAGGTGCA CGGCCCGCTT  
 9651 GACGGCGTAG TTTCGAGGC GCTGAAAGAG GTAGTTGAGG GTGGTGGCGG  
 CTGCCGCATC AAAGCGTCCG CGACTTTCTC CATCAACTCC CACCACCGCC  
 9701 TGTGTTCTGC CACGAAGAAG TACATAACCC AGCGTCGCAA CGTGGATTCTG  
 ACACAAGACG GTGCTTCTTC ATGTATTGGG TCGCAGCGTT GCACCTAAGC  
 9751 TTGATATCCC CCAAGGCCTC AAGGCGCTCC ATGGCCTCGT AGAAGTCCAC  
 AACTATAGGG GGTTCGGAG TTCCGCGAGG TACCGGAGCA TCTTCAGGTG  
 9801 GCGGAAGTTG AAAAAGTGGG AGTTGCGCGC CGACACGGTT AACTCCTCCT  
 CCGCTTCAAC TTTTGGACCC TCAACGCGCG GCTGTGCCAA TTGAGGAGGA  
 9851 CCAGAAGACG GATGAGCTCG GCGACAGTGT CGCGCACCTC GCGCTCAAAG  
 GGTCTTCTGC CTACTCGAGC CGCTGTACA GCGCGTGGAG CCGGAGTTTC  
 9901 GCTACAGGGG CCTCTTCTTC TTCTTCAATC TCCTCTTCCA TAAGGGCCTC  
 CGATGTCCCC GGAGAAGAAG AAGAAGTTAG AGGAGAAGGT ATTCCCGGAG  
 9951 CCGTCTTCT TCTTCTGGCG GCGGTGGGGG AGGGGGGACA CGGCGGCGAC  
 GGAAGAAGA AGAAGACCGC CGCCACCCCC TCCCCCTGT GCCGCCGCTG  
 10001 GACGGCGCAC CGGAGGGCGG TCGACAAAGC GCTCGATCAT CTCCCCGCGG  
 CTGCCGCGTG GCCCTCCGCC AGCTGTTTCG CGAGCTAGTA GAGGGGCGCC  
 10051 CGACGGCGCA TGCTCTCGGT GACGGCGCGG CCGTTCTCGC GGGGGCGCAG  
 GCTGCCGCGT ACCAGAGCCA CTGCCGCGCC GGCAAGAGCG CCCCCGCGTC  
 10101 TTGAAGACG CCGCCCGTCA TGTCGGGTT ATGGGTTGGC GGGGGGCTGC  
 AACCTTCTGC GCGGGGCGAGT ACAGGGCCAA TACCCAACCG CCCCCGACG  
 10151 CATGCGGCAG GGATACGGCG CTAACGATGC ATCTCAACAA TTGTTGTGTA  
 GTACGCCGTC CCTATGCCGC GATTGCTACG TAGAGTTGTT AACAACACAT  
 10201 GGTACTCCGC CGCCGAGGGA CCTGAGCGAG TCCGCATCGA CCGGATCGGA  
 CCATGAGGCG GCGGCTCCCT GGACTCGCTC AGGCGTAGCT GGCTAGCCT  
 10251 AAACCTCTCG AGAAAGGCGT CTAACGAGTC ACAGTCGCAA GGTAGGCTGA  
 TTTGGAGAGC TCTTCCGCA GATTGGTCAG TGTACGCGTT CCATCCGACT  
 10301 GCACCGTGGC GGGCGGCGAG GGGCGGCGGT CGGGTTGTT TCTGGCGGAG  
 CGTGGCACCG CCCGCCGTCG CCCGCCGCA GCCCAACAA AGACCGCCTC  
 10351 GTGCTGCTGA TGATGTAATT AAAGTAGGCG GTCTTGAGAC GCGGATGGT  
 CACGACGACT ACTACATTAA TTTCATCCGC CAGAACTCTG CCGCCTACCA

Figure 26 K

10401 CGACAGAAGC AATGTGTCCT TGGGTCCGGC CTGCTGAATG CGCAGGCTT  
 GCTGTCTTCG TGTACAGGA ACCCAGGCCG GACGACTTAC GCGTCCGCTA  
 10451 CGGCCATGCC CCAGGCTTCG TTTTGACATC GGCGCAGGTC TTTGTAGTAG  
 GCCGGTACGG GGTCCGAAGC AAAACTGTAG CCGCGTCCAG AAACATCATC  
 10501 TCTTGATGA GCCTTTCTAC CGGCACITCT TCTTCTCCTT CCTCTGTGCC  
 AGAACGTACT CGGAAAGATG GCCGTGAAGA AGAAGAGGAA GGAGAACAGG  
 10551 TGCATCTCTT GCATCTATCG CTGCGGCGGC GGCGGAGTTT GGCCGTAGGT  
 ACGTAGAGAA CGTAGATAGC GACGCCGCCG CCGCCTCAA CCAGCATCCA  
 10601 GGCGCCCTCT TCCTCCCATG CGTGTGACCC CGAAGCCCCT CATCGGCTGA  
 CCGCGGGAGA AGGAGGGTAC GCACACTGGG GCTTCGGGGA GTAGCCGACT  
 10651 AGCAGGGCTA GGTGCGCGAC AACCGGCTCG GCTAATATGG CCTGCTGCAC  
 TCGTCCCGAT CCAGCCGCTG TTGCGCGAGC CGATTATACC GGACGACGTG  
 10701 CTGCGTGAGG GTAGACTGGA AGTCATCCAT GTCCACAAAG CCGTGGTATG  
 GACGCACTCC CATCTGACCT TCAGTAGGTA CAGGTGTTTC GCCACCATAC  
 10751 CGCCCCGTGT GATGGTGTAA GTGCAGTTGG CCATAACGGA CCAGTTAACG  
 GCGGGCACAA CTACCACATT CACGTCAACC GGTATTGCCT GGTCAATTGC  
 10801 GTCTGGTGAC CCGGCTGCGA GAGCTCGGTG TACCTGAGAC GCGAGTAAGC  
 CAGACCACTG GGCCGACGCT CTCGAGCCAC ATGGACTCTG CGCTCATTCG  
 10851 CCTCGAGTCA AATACGTAGT CGTTGCAAGT CCGCACCAGG TACTGGTATC  
 GGAGCTCAGT TTATGCATCA GCAACGTTCA GGCGTGGTCC ATGACCATAG  
 10901 CCACCAAAAA GTGCGGCGGC GGCTGGCGGT AGAGGGGCCA GCGTAGGGTG  
 GGTGTTTTT CACGCCGCCG CCGACCGCCA TCTCCCCGT CCGATCCAC  
 10951 GCCGGGGCTC CGGGGGCGAG ATCTTCCAAC ATAAGGCGAT GATATCCGTA  
 CGGCCCGGAG GCGCCCGCTC TAGAAGGTTG TATTCCGCTA CTATAGGCAT  
 11001 GATGTACCTG GACATCCAGG TGATGCCGGC GGCGGTGGTG GAGGCGCGCG  
 CTACATGGAC CTGTAGGTCC ACTACGGCCG CCGCCACCAC CTCCGCGCGC  
 11051 GAAAGTCGCG GACGCGGTTT CAGATGTTGC GCAGCGGCAA AAAGTGCTCC  
 CTTTCAGCGC CTGCGCCAAG GTCTACAACG CGTCGCCGTT TTTACGAGG  
 11101 ATGGTCGGGA CGCTCTGGCC GGTGAGGCGC GCGCAATCGT TGACGCTCTA  
 TACCAGCCCT GCGAGACCGG CCAGTCCGCG CCGGTTAGCA ACTGCGAGAT  
 11151 GACCGTGCAA AAGGAGAGCC TGTAAAGCGG CACTCTTCCG TGGTCTGGTG  
 CTGGCACGTT TTCCTCTCGG ACATTGCCCC GTGAGAAGGC ACCAGACCAC  
 11201 GATAAATTTC CAAGGGTATC ATGGCGGACG ACCGGGGTTC GAGCCCCGTA  
 CTATTTAAGC GTTCCCATAG TACCGCTGCG TGGCCCCAAG CTCGGGGCAT  
 11251 TCCGGCCGTC CGCCGTGATC CATGCGGTTA CCGCCCGCGT GTCGAACCCA  
 AGGCCGGCAG GCGGCACTAG GTACGCCAAT GCGGGGCGCA CAGCTTGGGT  
 11301 GGTGTGCGAC GTCAGACAAC GGGGGAGTGC TCCTTTTGGC TTCCTTCCAG  
 CCACACGCTG CAGTCTGTTG CCCCTCACG AGGAAAACCG AAGGAAGGTC

Figure 26L

11351 GCGCGCGCGC TCGCGCTA GCTTTTTTGG CCACTGGCCG CGCGCACT  
 CGCGCCGCCG ACGACGCGAT CGAAAAAACC GGTGACCGGC GCGCGTCCCA  
 11401 AAGCGGTTAG GCTGGAAAGC GAAAGCATTA AGTGGCTCGC TCCCTGTAGC  
 TTCGCCAATC CGACCTTTCG CTTTCGTAAT TCACCGAGCG AGGGACATCG  
 11451 CGGAGGGTTA TTTTCCAAGG GTTGAGTCGC GGGACCCCGG GTTCGAGTCT  
 GCCTCCCAAT AAAAGGTTCC CAACTCAGCG CCCTGGGGGC CAAGCTCAGA  
 11501 CGGACCGGCC GGACTGCGGC GAACGGGGGT TTGCCTCCCC GTCATGCAAG  
 GCCTGGCCGG CCTGACGCCG CTTGCCCCCA AACGAGGGG CAGTACGTTT  
 11551 ACCCGGCTTG CAAATTCCTC CGGAAACAGG GACGAGCCCC TTTTGTGCTT  
 TGGGGCGAAC GTTTAAGGAG GCCTTTGTCC CTGCTCGGGG AAAAAACGAA  
 11601 TTCCAGATG CATCCGGTGC TGCGGCAGAT GCGCCCCCTT CCTCAGCAGC  
 AAGGGTCTAC GTAGGCCACG ACGCCGTCTA CGCGGGGGGA GGAGTCGTCTG  
 11651 GGCAAGAGCA AGAGCAGCGG CAGACATGCA GGGCACCCCTC CCCTCCTCCT  
 CCGTTCTCGT TCTCGTCGCC GTCTGTACGT CCCGTGGGAG GGGAGGAGGA  
 11701 ACCCGGTCAG GAGGGGCGAC ATCCGCGGTT GACGCGGCAG CAGATGGTGA  
 TGGCGCAGTC CTCCCCGCTG TAGGCGCCAA CTGCGCCGTC GTCTACCACT  
 11751 TTACGAACCC CGCGGCGGCC GGGCCCGGCA CTACCTGGAC TTGGAGGAGG  
 AATGCTTGGG GCGCGCGCGG CCCGGGCCGT GATGGACCTG AACCTCCTCC  
 11801 GCGAGGGCCT GCGCGGCTA GGAGCGCCCT CTCCTGAGCG GCACCCAAGG  
 CGCTCCCGGA CCGCGCCGAT CCTCGCGGGA GAGGACTCGC CGTGGGTTCC  
 11851 GTGCAGCTGA AGCGTGATAC GCGTGAGGCG TACGTGCCGC GGCAGAACCT  
 CACGTGCACT TCGCACTATG CGCACTCCGC ATGCACGGCG CCGTCTTGGA  
 11901 GTTTCGCGAC CGCGAGGGAG AGGAGCCCGA GGAGATGCGG GATCGAAAGT  
 CAAAGCGCTG GCGCTCCCTC TCCTCGGGCT CCTCTACGCC CTAGCTTTCA  
 11951 TCCACGCAGG GCGCGAGCTG CGGCATGGCC TGAATCGCGA GCGGTTGCTG  
 AGGTGCGTCC GCGGCTCGAC GCGTACCGG ACTTAGCGCT CGCCAACGAC  
 12001 CGCGAGGAGG ACTTTGAGCC CGACGCGCGA ACCGGGATTA GTCCCGCGCG  
 GCGCTCCTCC TGAAACTCGG GCTGCGCGCT TGGCCCTAAT CAGGGCGCGC  
 12051 CGCACACGTG GCGGCCGCCG ACCTGGTAAC CGCATACGAG CAGACGGTGA  
 GCGTGTGCAC CGCCGGCGGC TGGACCAATG GCGTATGCTC GTCTGCCACT  
 12101 ACCAGGAGAT TAACCTTCAA AAAAGCTTTA ACAACCACGT GCGTACGCTT  
 TGGTCTCTTA ATTGAAAGTT TTTTCGAAAT TGTGTTGCA CGCATGCGAA  
 12151 GTGGCGCGCG AGGAGGTGCG TATAGGACTG ATGCATCTGT GGGACTTTGT  
 CACCGCGCGC TCCTCCACCG ATATCCTGAC TACGTAGACA CCCTGAAACA  
 12201 AAGCGCGCTG GAGCAAAACC CAAATAGCAA GCCGCTCATG GCGCAGCTGT  
 TTCGCGCGAC CTCGTTTTGG GTTTATCGTT CGGCGAGTAC GCGCTCGACA  
 12251 TCCTTATAGT GCAGCACAGC AGGGACAACG AGGCATTGAG GGATGCGCTG  
 AGGAATATCA CGTCGTGTCG TCCTGTGTC TCCGTAAGTC CCTACGCGAC

Figure 26 M

12301 CTAACATAG T G C C C G A G G C C G C T G G C T G C T C G A T T T G A T A A T  
 G A T T T G T A T C A T T C G G G C T C C C G G C G A C C G A C G A G C T A A A C T A T T T G T A

12351 C C T G C A G A G C A T A G T G G T G C A G G A G C G C A G C T T G A G C C T G G C T G A C A A G G  
 G G A C G T C T C G T A T C A C C A C G T C C T C G C G T C G A A C T C G G A C C G A C T G T T C C

12401 T G G C C C C C A T C A A C T A T T C C A T G C T T A G C C T G G G C A A G T T T T A C G C C C C G  
 A C C G C G C G T A G T T G A T A A G T A C G A A T C G G A C C C G T T C A A A A T G C G G G C G

12451 A A G A T A T A C C A T A C C C C T T A C G T T C C C A T A G A C A A G G A G G T A A A G A T C G A  
 T T C T A T A T G G T A T G G G G A A T G C A A G G G T A T C T G T T C C T C C A T T T C T A G C T

12501 G G G G T T C T A C A T G C G C A T G G C G C T G A A G G T G C T T A C C T T G A G C G A C G A C C  
 C C C A A G A T G T A C G C G T A C C G C G A C T T C C A C G A A T G G A A C T C G C T G C T G G

12551 T G G G C G T T T A T C G C A A C G A G C G C A T C C A C A G C C G T G A G C G T G A G C C G G  
 A C C C G C A A A T A G C G T T G C T C G C G T A G G T G T T C C G G C A C T C G A C T C G G C C

12601 C G G C G C G A G C T C A G C G A C C G C G A G C T G A T G C A C A G C C T G C A A A G G G C C C T  
 C C C G C G C T C G A G T C G C T G G C G C T C G A C T A C G T G T C G G A C G T T T C C C G G G A

12651 G G C T G G C A C G G C A G C G C G A T A G A G A G G C C G A G T C C T A C T T T G A C G C G G  
 C C G A C C G T G C C G T C G C C G C T A T C T C T C C G G C T C A G G A T G A A A C T G C G C C

12701 G C G C T G A C C T G C G C T G G G C C C C A A G C C G A C G C C C C T G G A G G C A G C T G G G  
 C C G A C T G G A C C G A C C C G G G T T C G G C T G C G G G A C C T C C G T C G A C C C

12751 G C C G G A C C T G G C T G G C G G T G G C A C C C C G C G C G C T G G C A A C G T C G G C G G  
 C G G C C T G G A C C G A C C C C A C C G T G G G C G C G C G A C C G T T G C A G C C G C C

12801 C G T G G A G G A A T A T G A C G A G G A C G A T G A G T A C G A C C A G A G G A C G G C G A S T  
 G C A C C T C C T T A T A C T G C T C C T G C T A C T A T G C T G G T C T C T G C C G C T C A

12851 A C T A A G C G G T G A T G T T T C T G A T C A G A T G A T G C A A G A C G C A A C G G A C C C G G  
 T G A T T C G C C A C T A C A A A G A C T A G T C T A C T A C G T T C T G C G T T G C C T G G G C C

12901 C G G T G C G G G C G G C G C T G C A G A G C C A G C C G T C C G G C C T T A A C T C A C G G A C  
 G C C A C G C C C G C C G C G A C G T C T C G G T C G G C A G G C C G G A A T T G A G G T G C C T G

12951 G A C T G G C G C C A G G T C A T G G A C C G A T C A T G T C G C T G A C T G C G C A A T C C  
 C T G A C C G C G G T C C A G T A C C T G G C G T A G T A C A G C G A C T G A C G C G C T T A G G

13001 T G A C G C G T T C C G C A G C A G C C G A G G C C A C C G C T C T C C G C A A T T C T G G  
 A C T G C G C A A G G C C G T C G T C G G T C C G G T T G C C G A G A G G C G T T A A G A C C

13051 A A G C G G T G G T C C C G G C G C G C G C A A A C C C C A C G C A G A G A A G G T G C T G G C G  
 T T C G C C A C C A G G C C G C G C G C G T T G G G G T G C G T G C T C T T C C A G A C C G C

13101 A T C G T A A A C G C G C T G G C C G A A A C A G G G C C A T C C G G C C C G A C G A G G C C G G  
 T A G C A T T T G C G C A C C G G C T T T G T C C C G G T A G G C C G G G C T G C T C C G G C C

13151 C C T G G T C T A C G A C G C G T C C T T C A G C G C G T G G C T C G T T A C A A C A G C G G C A  
 G A C C A G A T G C T G C G C G A C G A A G T C G C G C A C C G A G C A A T G T T G T C G C C G T

13201 A C G T G C A G A C C A A C C T G G A C C G C T G G T G G G G A T G T G C G C G A G G C C G T G  
 T G C A C G T C T G G T G G A C C T G C C G A C C A C C T A C A C G C G C T C C G G C A C

Figure 26 N

13251 GCGCAGCGTG ACGCGCA GCAGCAGGGC AACCTGGGCT CCATGGC  
 CGCGTCGCAC TCGCGCGCGT CGTCGTCCCG TTGGACCCGA GGTACCAACG

13301 ACTAAACGCC TTCCTGAGTA CACAGCCCGC CAACGTGCCG CGGGGACAGG  
 TGATTTCGCG AAGGACTCAT GTGTCGGGCG GTTGCACGGC GCCCCTGTCC

13351 AGGACTACAC CAACCTTGTG AGCGCACTGC GGCTAATGGT GACTGAGACA  
 TCCTGATGTG GTTGAACAC TCGCGTGACG CCGATTACCA CTGACTCTGT

13401 CCGCAAAGTG AGGTGTACCA GTCTGGGCCA GACTATTTTT TCCAGACCAG  
 GCGGTTTCAC TCCACATGGT CAGACCCGGT CTGATAAAAA AGGTCTGGTC

13451 TAGACAAGGC CTGCAGACCG TAAACCTGAG CCAGGCTTTC AAAAATTGTC  
 ATCTGTTCGG GACGTCTGGC ATTTGGACTC GGTCCGAAAG TTTTGAACG

13501 AGGGGCTGTG GGGGGTGCGG GCTCCACAG GCGACCGCGC GACCGTGTCT  
 TCCCCGACAC CCCCCACGCC CGAGGGTGTG CGCTGGCGCG CTGGCACAGA

13551 AGCTTGCTGA CGCCCACTC GCGCCTGTTG CTGCTGCTAA TAGCGCCCTT  
 TCGAACGACT GCGGGTTGAG CGCGGACAA GACGACGATT ATCGCGGGAA

13601 CACGGACAGT GGCAGCGTGT CCCGGGACAC ATACCTAGGT CACTTGCTGA  
 GTGCCGTGCA CCGTCGCACA GGGCCCTGTG TATGGATCCA GTGAACGACT

13651 CACTGTACCG CGAGCCATA GGTGAGGCGC ATGTGGACGA GCATACTTTC  
 GTGACATGGC GCTCCGGTAT CCAGTCCGCG TACACCTGCT CGTATGAAAG

13701 CAGGAGATTA CAAGTGTCAG CCGCGCGCTG GGGCAGGAGG ACACGGGCAG  
 GTCTCTAAT GTTACAGTC GCGCGCGGAC CCCGTCTCC TGTGCCCCGTC

13751 CCTGGAGGCA ACCCTAAACT ACCTGCTGAC CAACCGGCGG CAGAAGATCC  
 GGACCTCCGT TGGGATTGTA TGACGACTG GTTGGCCGCC GTCTTCTAGG

13801 CCTCGTTGCA CAGTTTAAAC AGCGAGGAGG AGCGCATTTT GCGCTACGTG  
 GGAGCAACGT GTCAAATTTG TCGCTCCTCC TCGCGTAAAA CGCGATGCAC

13851 CAGCAGAGCG TGAGCCTTAA CCTGATGCGC GACGGGGTAA CGCCCAGCGT  
 GTCGTCTCGC ACTCGGAATT GGAATACCG CTGCCCCATT GCGGGTCGCA

13901 GCGGCTGGAC ATGACCGCGC GCAACATGGA ACCGGGCATG TATGCCTCAA  
 CCGCGACCTG TACTGGCGCG CGTTGTACCT TGGCCCGTAC ATACGGAGTT

13951 ACCGGCCGTT TATCAACCGC CTAATGGACT ACTTGCAATG CGCGGCCGCC  
 TGGCCGGCAA ATAGTTGGCG GATTACCTGA TGAACGTAGC GCGCCGGCGG

14001 GTGAACCCCG AGTATTTTAC CAATGCCATC TTGAACCCGC ACTGGCTACC  
 CACTTGGGGC TCATAAAGTG GTTACGGTAG AACTTGGGCG TGACCGATGG

14051 GCCCCCTGGT TTCTACACCG GGGGATTCGA GGTGCCCCGAG GGTAAACGATG  
 CGGGGGACCA AAGATGTGGC CCCCTAAGCT CCACGGGCTC CCATTGCTAC

14101 GATTCTCTG GACGACATA GACGACAGCG TGTTTTCCCC GCAACCGCAG  
 CTAAGGAGAC CTTGCTGTAT CTGCTGTGCG ACAAAGGGG CGTTGGCGTC

14151 ACCCTGCTAG AGTTGCAACA GCGCGAGCAG GCAGAGGCGG CGCTGCGAAA  
 TGGGACGATC TCAACGTTGT CCGCTCTGTC CGTCTCCGCC GCGACGCTTT

Figure 260

14201 GGAAAGCTTC CCGAGGCCAA GCAGCTTGTC CGATCTAGGC GCTGCCGACC  
CCTTTTGAAG GCTCCGGTT CGTCGAACAG GCTAGATCCG CGACGCAG

14251 CGCGGTGAGA TGCTAGTAGC CCATTTCCAA GCTTGATAGG GTCTCTTACC  
CGGCCAGTCT ACGATCATCG GGTAAAGGTT CGAACTATCC CAGAGAATGG

14301 AGCACTCGCA CCACCCGCCC GCGCCTGCTG GCGGAGGAGG AGTACCTAAA  
TCGTGAGCGT GGTGGGCGGG CGCGGACGAC CCGCTCCTCC TCATGGATTT

14351 CAACTCGCTG CTGCAGCCGC AGCGCGAAAA AAACCTGCCT CCGGCATTTT  
GTTGAGCGAC GACGTGCGCG TCGCGCTTTT TTTGGACGGA GGCCGTAAAG

14401 CCAACAACGG GATAGAGAGC CTAGTGGACA AGATGAGTAG ATGGAAGACG  
GGTTGTTGCC CTATCTCTCG GATCACCTGT TCTACTCATC TACCTTCTGC

14451 TACGCGCAGG AGCACAGGGA CGTGCCAGGC CCGCGCCCGC CCACCCGTCG  
ATGCGCGTCC TCGTGTCCCT GCACGGTCCG GCGCGGGCGG GGTGGGCAGC

14501 TCAAAGGCAC GACCGTCAGC GGGGTCTGGT GTGGGAGGAC GATGACTCGG  
AGTTTCCGTG CTGGCAGTCG CCCCAGACCA CACCCTCCTG CTACTGAGCC

14551 CAGACGACAG CAGCGTCTTG GATTGGGAG GGAGTGGCAA CCCGTTTGCG  
GTCTGCTGTC GTCGAGGAC CTAAACCTC CCTCACCGTT GGGCAAACGC

14601 CACCTTCGCC CCAGGCTGGG GAGAATGTTT TAAAAAATAA AAAAGCATGA  
GTGGAAGCGG GGTCGACCC CTCTTACAAA ATTTTTTTTT TTTTCGTACT

14651 TGCAAAATAA AAAACTCACC AAGGCCATGG CACCGAGCGT TGGTTTTCTT  
ACGTTTTATT TTTGAGTGG TTCCGGTACC GTGGCTCGCA ACCAAAAGAA

14701 GTATTTCCCT TAGTATGCGG CGCGCGGCGA TGTATGAGGA AGGTCTCTCT  
CATAAGGGGA ATCATACGCC GCGCGCCGCT ACATACTCCT TCCAGGAGGA

14751 CCTCTCTACG AGAGTGTGGT GAGCGCGGCG CCAAGTGGCGG CGGCGCTGGG  
GGGAGGATGC TCTCACACCA CTCGCGCCGC GGTACCCGCC GCCGCGACCC

14801 TTCTCCCTTC GATGCTCCCC TGGACCCGCC GTTTGTGCCT CCGCGGTACC  
AAGAGGGAAG CTACGAGGGG ACCTGGGCGG CAAACACGGA GCGGCCATGG

14851 TGCGGCCCTAC CGGGGGGAGA AACAGCATCC GTTACTCTGA GTTGGCACCC  
ACGCCGGATG GCGCCCTCT TTGTCGTAGG CAATGAGACT CAACCGTGGG

14901 CTATTCGACA CCACCCGTGT GTACCTGGTG GACAACAAGT CAACGGATGT  
GATAAGCTGT GGTGGGCACA CATGGACCAC CTGTTGTTCA GTTGCCCTACA

14951 GGCATCCCTG AACTACCAGA ACGACCACAG CAACTTTCTG ACCACGGTCA  
CCGTAGGGAC TTGATGGTCT TGCTGCTGTC GTTGAAAGAC TGGTGCCAGT

15001 TTCAAAACAA TGAATACAGC CCGGGGAGG CAAGCACACA GACCATCAAT  
AAGTTTGTG ACTGATGTCG GCGCCCTCC GTTCGTGTGT CTGGTAGTTA

15051 CTTGACGACC GGTGCGACTG GGGCGGCGAC CTGAAAACCA TCCTGCATAC  
GAAGTCTGCG CCAGCGTGAC CCGCGGCTG GACTTTTGGT AGGACGTATG

15101 CAACATGCCA AATGTGAACG AGTTCATGTT TACCAATAAG TTAAAGGCGC  
GTTGTACGGT TTACACTTGC TCAAGTACAA ATGGTTATTC AATTCCGCG

Figure 26 P

15151 GGGTGATGGT GCGCTTG CCTACTAAGG ACAATCAGGT GGAGCTLA  
 CCCACTACCA CAGCGCGAAC GGATGATTCC TGTAGTCCA CCTCGACTTT

15201 TACGAGTGGG TGGAGTTCAC GCTGCCCAGG GGCAACTACT CCGAGACCAT  
 ATGCTCAGCC ACCTCAAGTG CGACGGGCTC CCGTTGATGA GGCTCTGGTA

15251 GACCATAGAC CTTATGAACA ACGCGATCGT GGAGCACTAC TTGAAAGTGG  
 CTGGTATCTG GAATACTTGT TGCCTAGCA CCTCGTGATG AACTTTCACC

15301 GCAGACAGAA CGGGGTTCTG GAAAGCGACA TCGGGGTAAA GTTTGACACC  
 CGTCTGTCTT GCCCCAAGAC CTTTCGCTGT AGCCCCATT CAAACTGTGG

15351 CGCAACTTCA GACTGGGGTT TGACCCCGTC ACTGGTCTTG TCATGCCTGG  
 GCGTTGAAGT CTGACCCCAA ACTGGGGCAG TGACCAGAAC AGTACGGACC

15401 GGTATATACA AACGAAGCCT TCCATCCAGA CATCATTTTG CTGCCAGGAT  
 CCATATATGT TTGCTTCGCA AGGTAGGTCT GTAGTAAAC GACGGTCTTA

15451 GCGGGGTGGA CTTACCCAC AGCCGCCTGA GCAACTTGT GGGCATCCGC  
 CGCCCCACCT GAAGTGGGTG TCGCGGACT CGTGAACAA CCGTAGGCG

15501 AAGCGGCAAC CCTTCCAGGA GGGCTTTAGG ATCACCTACG ATGATCTGGA  
 TTCGCCGTTG GGAAGGTCTT CCGAAATCC TAGTGGATGC TACTAGACCT

15551 GGGTGGTAAC ATTCCCGCAC TGTGGATGT GGACGCCTAC CAGGCGAGCT  
 CCCACCATTG TAAGGGCGTG ACAACCTACA CTTGCGGATG GTCCGCTCGA

15601 TGAAAGATGA CACCGAACAG GCGGGGGTG GCGCAGGCG CAGCAACAGC  
 ACTTCTACT GTGGCTTGT CCGCCCCAC CGCGTCCGC GTCGTTGTCG

15651 AGTGGCAGCG GCGCGGAAGA GAACTCCAAC GCGGCAGCCG CGGCAATGCA  
 TCACCGTCGC CGCGCCTTCT CTTGAGGTTG CGCCGTCGCG GCCGTTACGT

15701 CCCGGTGGAG GACATGAACG ATCATGCCAT TCGCGGCGAC ACCTTTGCCA  
 CGGCCACCTC CTGTACTTGC TAGTACGGTA AGCGCCGCTG TGGAAACGGT

15751 CACGGGCTGA GGAGAAGCG GCTGAGGCCG AAGCAGCGGC CGAAGCTGCC  
 GTGCCGACT CTTCTTCGCG CGACTCCGCG TTCGTCGCGG GTTCGACGG

15801 GCCCCCGCTG CGCAACCCGA GGTGAGAAG CCTCAGAAGA AACCAGTGAT  
 CGGGGGCGAC GCGTTGGGCT CCAGCTCTTC GGAGTCTTCT TTGGCCACTA

15851 CAAACCCCTG ACAGAGGACA GCAAGAAACG CAGTTACAAC CTAATAAGCA  
 GTTTGGGGAC TGCTCTCTGT CGTCTTTGCG GTCAATGTTG GATTATTCGT

15901 ATGACAGCAC CTTACCCAG TACCGCAGCT GGTACCTTGC ATACAACTAC  
 TACTGTCTGT GAAGTGGGTC ATGGCGTCA CCATGGAACG TATGTTGATG

15951 GCGGACCCCTC AGACCGGAAT CCGCTCATGG ACCCTGCTTT GCACTCCTGA  
 CCGCTGGGAG TCTGGCCCTA GCGAGTACC TGGGACGAAA CGTGAGGACT

16001 CGTAACCTGC GGCTCGGAGC AGGTCTACTG GTCGTTGCCA GACATGATGC  
 GCATTGGACG CCGAGCCTCG TCCAGATGAC CAGCAACGGT CTGTACTACG

16051 AAGACCCCGT GACCTTCCGC TCCACGCGCC AGATCAGCAA CTTTCCGGTG  
 TTCTGGGGCA CTGGAAGGCG AGGTGCGCGG TCTAGTCGTT GAAAGGCCAC

Figure 26 Q

16101 GTGGGCGCGG A TGTGTC CGTGCACTCC AAGAGCTTCT ACAACCTCA  
CACCCGCGGC TACAACGG GCACGTGAGG TTCTCGAAGA TGTGCTCT

16151 GGCCGTCTAC TCCCAACTCA TCCGCCAGTT TACCTCTCTG ACCCAGTGT  
CCGGCAGATG AGGGTTGAGT AGGCGGTCAA ATGGAGAGAC TGGGTGCACA

16201 TCAATCGCTT TCCCGAGAAC CAGATTTTGG CGCGCCCGCC AGCCCCCACC  
AGTTAGCGAA AGGGCTCTTG GTCTAAAACC GCGCGGGCGG TCGGGGGTGG

16251 ATCACCACCG TCAGTGA AAA CGTTCCTGCT CTCACAGATC ACGGGACGCT  
TAGTGGTGGC AGTCACTTTT GCAAGGACGA GAGTGTCTAG TGCCCTGCGA

16301 ACCGCTGCGC AACAGCATCG GAGGAGTCCA GCGAGTGACC ATTACTGACG  
TGGCGACGCG TTGTCGTAGC CTCCTCAGGT CGCTCACTGG TAATGACTGC

16351 CCAGACGCGC CACCTGCCCC TACGTTTACA AGGCCCTGGG CATAGTCTCG  
GGTCTGCGGC GTGGACGGGG ATGCAAAATGT TCCGGGACCC GTATCAGAGC

16401 CCGCGCGTCC TATCGAGCCG CACTTTTTGA GCAAGCATGT CCATCCTTAT  
GCGCGCGCAGG ATAGCTCGGC GTGAAAACT CGTTCGTACA GGTAGGAATA

16451 ATCGCCCGAGC AATAACACAG GCTGGGGCCT GCGCTTCCCA AGCAAGATGT  
TAGCGGGTCG TTATTGTGTC CGACCCCGGA CGCGAAGGGT TCCTTCTACA

16501 TTGGCGGGGC CAAGAAGCGC TCCGACCAAC ACCCAGTGGC CGTGCGCGGG  
AACCGCCCGG GTTCTTCGCG AGGCTGGTTG TGGGTACGC GCACGCGCCC

16551 CACTACCGCG CGCCCTGGGG CGCGCACAAA CGCGGCCGCA CTGGGCGCAC  
GTGATGGCGC GCGGGACCCC GCGCGTGTTC GCGCCGGCGT GACCCGCGTG

16601 CACCGTCGAT GACGCCATCG ACGCGGTGGT GGAGGAGGCG CGCAACTACA  
GTGGCAGCTA CTGCGGTAGC TGCGCCACCA CCTCCTCCGC GCGTTGATGT

16651 CGCCACGCGC GCCACCAAGT TCCACAGTGG ACGCGGCCAT TCAGACCGTG  
GCGGGTGGG CGGTGGTCAC AGGTGTCACC TGCGCCGGTA AGTCTGGCAC

16701 GTGCGCGGAG CCCGCGCTA TGCTAAAATG AAGAGACGGC GGAGGCGCGT  
CACGCGCCTC GGGCCGCGAT ACGATTTTAC TTCTCTGCCG CCTCCGCGCA

16751 AGCACGTGCG CACCGCCGCC GACCCGGCAC TGCCGCCCAA CGCGCGCGCG  
TCGTGCAGCG GTGGCGGCGG CTGGGCCGTG ACGCGGGTT GCGCGCCGCC

16801 CGGCCCTGCT TAACCGCGCA CGTCGCACCG GCCGACGGC GGCCATGCGG  
GCCGGGACGA ATTGGCGCGT GCAGCGTGGC CGGCTGCCCC CCGGTACGCC

16851 GCGCTCGAA GGCTGGCCGC GGGTATTGTC ACTGTGCCCC CCAGGTCCAG  
CGCGGAGCTT CCGACCGCGC CCCATAACAG TGACACGGGG GGTCCAGGTC

16901 GCGACGAGCG GCCGCCGAG CAGCCGCGGC CATTAGTGCT ATGACTCAGG  
CGCTGCTCGC CGGCGGCGTC GTCGGCGCGG GTAATCACGA TACTGAGTCC

16951 GTCGACGGGG CAACGTGTAT TGGGTGCGCG ACTCGGTTAG CGGCCTGCGC  
CAGCGTCCCC GTTGACATA ACCCACGCGC TGAGCCAATC GCCGGACGCG

17001 GTGCCCCGTG GCACCCGCCC CCCGCGCAAC TAGATTGCAA GAAAAACTA  
CACGGGCACG CGTGGGCGGG GGGCGCGTTG ATCTAACGTT CTTTTTGTAT

Figure 26R

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17051 CTTAGACTCG TTTGTTGTA TGTATCCAGC GCGGGCGGCG CGLAALTTG
      GAATCTGAGC ATGACAACAT ACATAGGTCG CCGCCGCCCG GCGTTGCTTC

17101 CTATGTCCAA GCGCAAAATC AAAGAAGAGA TGCTCCAGGT CATCGCGCCG
      GATACAGGTT CGCGTTTCTAG TTTCTTCTCT ACGAGGTCCA GTAGCGCGGC

17151 GAGATCTATG GCCCCCCGAA GAAGGAAGAG CAGGATTACA AGCCCCGAAA
      CTCTAGATAC CGGGGGGCTT CTTCTTCTCT GTCCTAATGT TCGGGGCTTT

17201 GCTAAAGCGG GTCAAAAAGA AAAAGAAAGA TGATGATGAT GAACTTGACG
      CGATTTCCGC CAGTTTTTCT TTTTCTTCT ACTACTACTA CTTGAACTGC

17251 ACGAGGTGGA ACTGCTGCAC GCTACCGCGC CCAGGCGACG GGTACAGTGG
      TGCTCCACCT TGACGACGTG CGATGGCGCG GGTCCGCTGC CCATGTCACC

17301 AAAGGTCGAC GCGTAAAACG TGTTTTGCGA CCGGCGACCA CCGTAGTCTT
      TTTCCAGCTG CGCATTTTGC ACAAACGCT GGGCCGTGGT GGCATCAGAA

17351 TACGCCCCGT GAGCGCTCCA CCCGCACCTA CAAGCGCGTG TATGATGAGG
      ATGCGGGCCA CTCGCGAGGT GGGCGTGGAT GTTCGCGCAC ATACTACTCC

17401 TGTACGSCGA CGAGGACCTG CTTGAGCAGG CCAACGAGCG CCTCGGGGAG
      ACATGCCGCT GCTCCTGGAC GAACTCGTCC GGTGCTCGC GGAGCCCCTC

17451 TTTGCCCTACG GAAAGCGGCA TAAGGACATG CTGGCGTTGC CGCTGGACGA
      AAACGGATGC CTTTCGCCGT ATTCTGTAC GACCGCAACG GCGACCTGCT

17501 GGGCAACCCA ACACCTAGCC TAAAGCCCGT AACACTGCAG CAGGTGCTGC
      CCCGTGCGGT TGTGGATCGG ATTTCCGGCA TTGTGACGTC GTCCACGACG

17551 CCGCGCTTGC ACCGTCCGAA GAAAAGCGCG GCCTAAAGCG CGAGTCTGGT
      GGGCGGAACG TGGCAGGCTT CTTTTCGCGC CGGATTTCCG GCTCAGACCA

17601 GACTTGSCAC CCACCGTGCA GCTGATGGTA CCCAAGCGCC AGCGACTGGA
      CTGAACCGTG GGTGGCACGT CGACTACCAT GGGTTCGCGG TCGTGACCT

17651 AGATGTCTTG GAAAAATGA CCGTGGAACC TGGGCTGGAG CCCGAGGTCC
      TCTACAGAAC CTTTTTACT GGCACCTGG ACCCGACCTC GGGCTCCAGG

17701 GCGTGCGGCC AATCAAGCAG GTGGCGCCGG GACTGGGCGT GCAGACCGTG
      CGCACGCCGG TTAGTTCGTC CACCGCGGCC CTGACCCGCA CGTCTGGCAC

17751 GACGTTGAGA TACCCACTAC CAGTAGCACC AGTATTGCCA CCGCCACAGA
      CTGCAAGTCT ATGGGTGATG GTCATCGTGG TCATAACGGT GCGGGTGTCT

17801 GGGCATGGAG ACACAAACGT CCCCGGTTGC CTCAGCGGTG GCGGATGCCG
      CCCGTACCTC TGTGTTTCCA GGGGCCAACG GAGTCGCCAC CGCCTACGGC

17851 CGGTGCAGGC GGTGCTGCG GCCGCGTCCA AGACCTCTAC GGAGGTGCAA
      GCCACGTCCG CCAGCGACGC CGCGCAGGT TCTGGAGATG CCTCCACGTT

17901 ACGGACCCGT GGATGTTTCC CGTTTCAGCC CCCCAGCGCC CGCGCCGTTT
      TGCCTGGCA CCTACAAAGC GCAAAGTCGG GGGGCCGCGG GCGCGCAAG

17951 GAGGAAGTAC GGGCCCGCCA GCGCGCTACT GCCCGAATAT GCCCTACATC
      CTCCTTCATG CCGCGCGGT CCGCGCATGA CCGGCTTATA CGGGATGTAG

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Figure 265

18001 CTTCCATTGC GCTACCCCCC GGCTATCGTG GCTACACCTM CCGGCCGCTEA  
GAAGGTAACG CATTGGGGG CCGATAGCAC CGATGTGGAT GCGGGCTT

18051 AGACGAGCAA CTACCCGACG CCGAACCACC ACTGGAACCC GCCGCCGCCG  
TCTGCTCGTT GATGGGCTGC GGCTTGGTGG TGACCTTGGG CCGCGCGGGC

18101 TCGCCGTCGC CAGCCCCGTC TGGCCCCGAT TTCCGTGCGC AGGGTGGCTC  
ACCGGCACCG GTCGGGCACG ACCGGGGCTA AAGGCACCG TCCCACCGAG

18151 GCGAAGGAGG CAGGACCCTG GTGCTGCCAA CAGCGCGCTA CCACCCACG  
CGCTTCCTCC GTCTGGGAC CACGACGGT GTGCGCGCAT GGTGGGGTGC

18201 ATCGTTTAAA AGCCGGTCTT TGTGGTCTT GCAGATATGG CCCTCACCTG  
TAGCAAATTT TCGGCCAGAA ACACCAAGAA CGTCTATACC GGGAGTGGAC

18251 CCGCCTCCGT TTCCCGGTGC CGGGATTCCG AGGAAGAATG CACCGTAGGA  
GGCGGAGGCA AAGGGCCACG GCCCTAAGGC TCCTTCTTAC GTGGCATCCT

18301 GGGGCATGGC CGGCCACGGC CTGACGGGCG GCATGCGTCG TCGCACCCAC  
CCCCGTACCG GCCGGTGGCG GACTGCCCCG CGTACGCAGC ACGCGTGGTG

18351 CGCGCGCGGC GCGCGTCGCA CCGTCGCATG CGCGCGGTA TCCTGCCCTT  
GCCGCCGCGG CCGCGAGCGT GGCAGCGTAC GCGCCGCCAT AGGACGGGGA

18401 CCTTATTCCA CTGATCGCCG CCGCGATTGG CGCCGTGCCC GGAATTGCAT  
GGAATAAGGT GACTAGCGGC GCCGCTAACC GCGGCACGGG CCTTAACGTA

18451 CCGTGGCCTT GCAGGCGCAG AGACACTGAT TAAAAACAAG TTGCATGTGG  
GGCACC GGAA CGTCCGCGTC TCTGTGACTA ATTTTGTTC AACGTACACC

18501 AAAAATCAAA ATAAAAAGTC TGGACTCTCA CGCTCGCTTG GTCCTGTAAC  
TTTTTAGTTT TATTTTTCAG ACCTGAGAGT GCGAGCGAAC CAGGACATTG

18551 TATTTTGTAG AATGGAAGAC ATCAACTTTG CGTCTCTGGC CCCGCGACAC  
ATAAAACATC TTACCTTCTG TAGTTGAAAC GCAGAGACCG GGGCGCTGTG

18601 GGCTCGCGCC CGTTCATGGG AAAC TG GCAA GATATCGGCA CCAGCAATAT  
CCGAGCGCGG GCAAGTACCC TTTGACCGTT CTATAGCCGT GGTGCTTATA

18651 GAGCGGTGGC GCCTTCAGCT GGGGCTCGCT GTGGAGCGGC ATTAAAAATT  
CTCGCCACCG CGGAAGTCCA CCCCAGCGCA CACCTCGCCG TAATTTTAA

18701 TCGGTTCAC CGTTAAGAAC TATGGCAGGA AGGCCTGGAA CAGCAGCACA  
AGCCAAGGTG GCAATTCTTG ATACCGTCGT TCCGGACCTT GTCGTCTGT

18751 GGCCAGATGC TGAGGGATAA GTTGAAAGAG CAAAATTTCC AACAAAAGGT  
CCGGTCTACG ACTCCCTATT CAACTTTCTC GTTTTAAAGG TTGTTTTC

18801 GGTAGATGGC CTGGCCTCTG GCATTAGCGG GGTGGTGGAC CTGGCCAACC  
CCATCTACCG GACCGGAGAC CGTAATCGCC CCACCACCTG GACCGGTGG

18851 AGGCAGTGCA AAATAAGATT AACAGTAAGC TTGATCCCCG CCCTCCCGTA  
TCCGTACAGT TTTATTCTAA TTGTCAATCG AACTAGGGGC GGGAGGGCAT

18901 GAGGAGCCTC CACCGGCCGT GGAGACAGTG TCTCCAGAGG GCGGTGGCGA  
CTCCTCGGAG GTGGCCGCA CCTCTGTCAC AGAGGTCTCC CCGCACCGCT

Figure 26T

18951 AAAGCGTCCG C CCGACA GGAAGAAGAC TCTGGTGACG CAAATAC G  
TTTCGACGGC GCGGGCTGT CCTTCTTTG AGACCACTGC GTTTATC G

19001 AGCCTCCCTC GTACGAGGAG GCACTAAAGC AAGGCCTGCC CACCACCCGT  
TCGGAGGGAG CATGCTCCTC CGTGATTTG TTCCGGACGG GTGGTGGGCA

19051 CCCATCGCGC CCATGGCTAC CGGAGTGCTG GGCCAGCACA CACCCGTAAC  
GGGTAGCGCG GGTACCGATG GCCTCACGAC CCGGTCGTGT GTGGGCATTG

19101 GCTGGACCTG CCTCCCCCG CCGACACCCA GCAGAAACCT GTGCTGCCAG  
CGACCTGGAC GGAGGGGGG GGTGTGGGT CGTCTTTGGA CACGACGGTC

19151 GCCCCACCGC CGTTGTGTGA ACCCGTCTTA GCCGCGCGTC CCTGCGCCGC  
CGGGCTGGCG GTAACAACAT TGGGCAGGAT CGGCGCGCAG GGACGCGGCG

19201 GCCGCCAGCG GTCCGCGATC GTTGC GGCC GTAGCCAGTG GCAACTGGCA  
CGGCGGTGCG CAGGCGCTAG CAACGCCGGG CATCGGTCAC CGTTGACCGT

19251 AAGCACACTG AACAGCATCG TGGGTCTGGG GGTGCAATCC CTGAAGCGCC  
TTCGTGTGAC TTGTCTGAGC ACCCAGACCC CCACGTTAGG GACTTCGCGG

19301 GACGATGCTT CTGATAGCTA ACGTGTCGTA TGTGTGTGTCAT GTATGCGTCC  
CTGCTACGAA GACTATCGAT TGCACAGCAT ACACACAGTA CATACGCAGG

19351 ATGTCGCCGC CAGAGGAGCT GGTGAGCCGC CGCGCGCCCG CTTTCCAAGA  
TACAGCGGCG GTCTCCTCGA CGACTCGGCG CGCGCGCGGC GAAAGGTTCT

19401 TGGCTACCCC TTCGATGATG CCGCAGTGGT CTTACATGCA CATCTCGGGC  
ACCGATGGGG AAGCTACTAC GGCGTCACCA GAATGTACGT GTAGAGCCCC

19451 CAGGACGCCT CGGAGTACCT GAGCCCCGGG CTGGTGCACT TTGCCCCGCG  
GTCTGCGGA GCCTCATGGA CTCGGGGCCC GACCACGTCA AACGGGCGCG

19501 CACCGAGACG TACTTCAGCC TGAATAACAA GTTTAGAAAC CCCACGGTGG  
GTGGCTCTGC ATGAAGTCGG ACTTATTGTT CAAATCTTTG GGGTGCCACC

19551 CGCCTACGCA CGACGTGACC ACAGACCGGT CCCAGCGTPT GACGCTGCGG  
CGGGATGCGT GCTGCACTGG TGTCTGGCCA GGGTCGCAAA CTGCGACGCC

19601 TTCATCCCTG TGGACCGTGA GGATACTGCG TACTCTGACA AGGCGCGGTT  
AAGTAGGGAC ACCTGGCACT CCTATGACGC ATGAGCATGT TCCGCGCCAA

19651 CACCCTAGCT GTGGGTGATA ACCGTGTGCT GGACATGGCT TCCACGTACT  
GTGGGATCGA CACCCACTAT TGGCACACGA CCTGTACCGA AGGTGCATGA

19701 TTGACATCCG CGGCGTGCTG GACAGGGGCC CTACTTTTAA GCCCTACTCT  
AACTGTAGGC GCCGCACGAC CTGTCCCCGG GATGAAAATT CGGGATGAGA

19751 GGCCTGCCT ACAACGCCCT GGCTCCCAAG GGTGCCCAA ATCCTTGCGA  
CCGTGACGGA TGTTCGGGA CCGAGGGTTC CCACGGGGTT TAGGAACGCT

19801 ATGGGATGAA CCGTCTACTG CTCTTGAAAT AAACCTAGAA GAAGAGGACG  
TACCTACTT CGACGATGAC GAGAACTTA TTTGGATCTT CTTCTCCTGC

19851 ATGACAACGA AGACGAAGTA GACGAGCAAG CTGAGCAGCA AAAAATCAC  
TACTGTTGCT TCTGCTTCAT CTGCTCGTTC GACTCGTCGT TTTTGTAGTG

Figure 26 u

19901 GTATTTGGGC A GCGCTTA TTCTGGTATA AATATTACAA AGGAGG T  
CATAAACCCG TCCGCGGAAT AAGACCATAT TTATAATGTT TCCTCCCAT

19951 TCAAATAGGT GTCGAAGGTC AAACACCTAA ATATGCCGAT AAAACATTTT  
AGTTTATCCA CAGCTTCCAG TTTGTGGATT TATACGGCTA TTTTGTAAAG

20001 AACCTGAACC TCAAATAGGA GAATCTCAGT GGTACGAAAC AGAAATTAAT  
TTGGACTTGG AGTTTATCCT CTTAGAGTCA CCATGCTTTG TCTTTAATTA

20051 CATGCAGCTG GGAGAGTCCT AAAAAAGACT ACCCCAATGA AACCATGTTA  
GTACGTCGAC CCTCTCAGGA TTTTCTCTGA TGGGGTTACT TTGGTACAAT

20101 CGGTTTCATAT GCAAAACCCA CAAATGAAAA TGGAGGGCAA GGCATTCTTG  
GCCAAGTATA CGTTTGGGT GTTACTTTT ACCTCCCGTT CCGTAAGAAC

20151 TAAAGCAACA AAATGGAAAG CTAGAAAGTC AAGTGGAAAT GCAATTTTTC  
ATTTGCTTGT TTTACCTTTC GATCTTTCAG TTCACCTTTA CGTTAAAAAG

20201 TCAACTACTG AGGCAGCCGC AGGCAATGGT GATAACTTGA CTCCTAAAGT  
AGTTGATGAC TCCGTCGGCG TCCGTTACCA CTATTGAAT GAGGATTTCA

20251 GGTATTGTAC AGTGAAGATG TAGATATAGA AACCCAGAC ACTCATATTT  
CCATAACATG TCACTTCTAC ATCTATATCT TTGGGGTCTG TGAGTATAAA

20301 CTTACATGCC CACTATTAAG GAAGGTAAT CACGAGAACT AATGGGCCAA  
GAATGTACGG GTGATAATC CTTCCATTGA GTGCTCTTGA TTACCCGTT

20351 CAATCTATGC CCAACAGGCC TAATTACATT GCTTTTAGGG ACAATTTTAT  
GTTAGATACG GGTGTCCGG ATTAATGTAA CGAAATCCC TGTTAAAAATA

20401 TGGTCTAATG TATTACAACA GCACGGGTAA TATGGGTGTT CTGGCGGGCC  
ACCAGATTAC ATAATGTTGT CGTGCCCAT ATACCCACAA GACCGCCCGG

20451 AAGCATCGCA GTTGAATGCT GTTGTAGATT TGCAAGACAG AAACACAGAG  
TTGCTAGCGT CAACTTACGA CAACATCTAA ACGTTCTGTC TTTGTGCTC

20501 CTTTCATACC AGCTTTTGCT TGATTCCATT GGTGATAGAA CCAGGTACTT  
GAAAGTATGG TCGAAAACGA ACTAAGGTAA CCACTATCTT GGTCCATGAA

20551 TTCTATGTGG AATCAGGCTG TTGACAGCTA TGATCCAGAT GTTAGAATTA  
AAGATACACC TTAGTCCGAC AACTGTGAT ACTAGGTCTA CAATCTTAAT

20601 TTGAAATCA TGGAACGAA GATGAACCTC CAAATTACTG CTTTCCACTG  
AACTTTTAGT ACCTTGACTT CTACTTGAAG GTTAAATGAC GAAAGGTGAC

20651 GGAGGTGTGA TTAATACAGA GACTCTTACC AAGGTAAAAC CTAAAACAGG  
CCTCCACACT AATATGTCT CTGAGAATGG TTCCATTTTG GATTTTGTCC

20701 TCAGGAAAT GGATGGGAAA AAGATGCTAC AGAATTTTCA GATAAAAATG  
AGTCCTTTTA CCTACCTTT TTCTACGATG TCTTAAAGT CTATTTTAC

20751 AAATAAGAGT TGGAAATAAT TTTGCCATGG AAATCAATCT AAATGCCAAC  
TTTATTCTCA ACCTTTATTA AAACGGTACC TTTAGTTAGA TTTACGGTTG

20801 CTGTGGAGAA ATTTCTGTG CTCCAACATA GCGCTGTATT TGCCCGACAA  
GACACCTCTT TAAAGGACAT GAGGTGTAT CCGACATAA ACGGGCTGTT

Figure 26 v

20851 GCTAAAGTAC AGCTCTTCCA ACGTAAAAAT TTCTGATAC CCAAACTT  
 CGATTTTCATG TGGGAAGGT TGCATTTTPTA AAGACTATTG GGTTTGGA  
 20901 ACGACTACAT GAACAAGCGA GTGGTGGCTC CCGGGCTAGT GGACTGCTAC  
 TGCTGATGTA CTGTGTCGCT CACCACCGAG GGCCCGATCA CCTGACGATG  
 20951 ATTAACCTTG GAGCACGCTG GTCCCTTGAC TATATGGACA ACGTCAACCC  
 TAATTGGAAC CTCGTGCGAC CAGGGAACGT ATATACCTGT TGCAGTTGGG  
 21001 ATTTAACCAC CACCGCAATG CTGGCCTGCG CTACCGCTCA ATGTTGCTGG  
 TAAATTGGTG GTGGCGTTAC GACCGGACGC GATGGCGAGT TACAACGACC  
 21051 GCAATGGTCG CTATGTGCCC TTCCACATCC AGGTGCCTCA GAAGTTCTTT  
 CGTTACCAGC GATACACGGG AAGGTGTAGG TCCACGGAGT CTTCAAGAAA  
 21101 GCCATTAAAA ACCTCCTTCT CCTGCCGGGC TCATACACCT ACGAGTGGA  
 CGGTAATTTT TGGAGGAAGA GGACGGCCCG AGTATGTGGA TGCTCACCTT  
 21151 CTTCAGGAAG GATGTTAACA TGGTTCTGCA GAGCTCCCTA GGAAATGACC  
 GAAGTCCTTC CTACAATTGT ACCAAGACGT CTCGAGGGAT CCTTTACTGG  
 21201 TAAGGGTTGA CGGAGCCAGC ATTAAGTTTG ATAGCATTTG CCTTTACGCC  
 ATTCCCAACT GCCTCGGTG TAATTCAAAC TATCGTAAAC GGAAATGCGG  
 21251 ACCTTCTTCC CCATGGCCCA CAACACCGCC TCCACGCTTG AGGCCATGCT  
 TGGAGAAGG GGTACCGGGT GTTGTGGCGG AGGTGCGAAC TCCGGTACGA  
 21301 TAGAAACGAC ACCAACGACC AGTCCTTTAA CGACTATCTC TCCGCCGCA  
 ATCTTTGCTG TGGTTGCTGG TCAGGAAATT GCTGATAGAG AGGCGCGGGT  
 21351 ACATGCTCTA CCCTATACCC GCCAACGCTA CCAACGTGCC CATATCCATC  
 TGTACGAGAT GGGATATGGG CGGTGCGAT GGTGACCGG STATAGGTAG  
 21401 CCCTCCCGCA ACTGGGCGGC TTTCGCGGC TGGGCCTTCA CGCGCCTTAA  
 GGGAGGGCGT TGACCCGCGG AAAGGCGCGG ACCCGGAAGT GCGCGGAATT  
 21451 GACTAAGGAA ACCCCATCAC TGGGCTCGGG CTACGACCTT TATTACACCT  
 CTGATTCCTT TGGGGTAGTG ACCCGAGCCC GATGCTGGGA ATAATGTGGA  
 21501 ACTCTGGCTC TATACCTTAC CTAGATGGAA CCTTTTACCT CAACCACACC  
 TGAGACCGAG ATATGGGATG GATCTACCTT GGAAATGGA GTTGGTGTGG  
 21551 TTAAAGAAGG TGGCCATTAC CTTTGACTCT TCTGTCAGCT GGCCTGGCAA  
 AAATTCTTCC ACCGGTAATG GAAACTGAGA AGACAGTCGA CCGGACCGTT  
 21601 TGACCGCCTG CTTACCCCA ACGAGTTTGA AATTAAGCGC TCAGTTGACG  
 ACTGGCGGAC GAATGGGGGT TGCTCAAAC TTAATTGCGG AGTCAAACGTC  
 21651 GGGAGGGTTA CAACGTTGCC CAGTGTAACA TGACCAAAGA CTGGTTCTCG  
 CCTCCCAAT GTTGCAACGG GTCACATTGT ACTGGTTTCT GACCAAGGAC  
 21701 GTACAAATGC TAGCTAATA TAACATTGGC TACCAGGGCT TCTATATCCC  
 CATGTTTACG ATCGATTGAT ATTGTAACCG ATGGTCCCGA AGATATAGGG  
 21751 AGAGAGCTAC AAGGACCGCA TGTACTCCTT CTTTAGAAAC TTCCAGCCCA  
 TCTCTCGATG TTCCTGGCGT ACATGAGGAA GAAATCTTTG AAGGTGCGGT

Figure 26 W

21801 TGAGCCGTCA GGTGGTGGAT GATACTAAAT ACAAGGAATA CGAACATG  
ACTCGGCAGT CACCTA CTATGATTTA TGTTCCTGAT GGTGT C

21851 GGCATCCTAC ACCAACACAA CAACTCTGGA TTTGTGGCT ACCTTGCCCC  
CCGTAGGATG TGGTTGTGTT GTTGAGACCT AAACAACCGA TGAACGGGG

21901 CACCATGCGC GAAGGACAGG CCTACCCTGC TAACTTCCCC TATCCGCTTA  
GTGGTACGCG CTTCTGTGCC GGATGGGACG ATTGAAGGGG ATAGGCGAAT

21951 TAGGCAAGAC CGCAGTTGAC AGCATTACCC AGAAAAAGTT TCTTTGCGAT  
ATCCGTTCTG GCGTCAACTG TCGTAATGGG TCTTTTCAA AGAAACGCTA

22001 CGCACCCCTT GGGCATCCC ATTCTCCAGT AACTTTATGT CCATGGGCGC  
GCGTGGGAAA CCGGTAGGG TAAGAGGTCA TTGAAATACA GGTACCCGCG

22051 ACTCACAGAC CTGGGCCAAA ACCTTCTCTA CGCCAACTCC GCCCACGCGC  
TGAGTGTCTG GACCCGGTTT TGAAGAGAT GCGGTTGAGG CGGGTGCGCG

22101 TAGACATGAC TTTTGAGGTG GATCCCATGG ACGAGCCAC CCTTCTTAT  
ATCTGTACTG AAAACTCCAC CTAGGGTACC TGCTCGGGTG GGAAGAAATA

22151 GTTTTGTGTTG AAGTCTTTGA CGTGGTCCGT GTGCACCAGC CGCACCGCGG  
CAAAACAAAC TTCAGAACT GCACCAGGCA CACGTGGTCG GCGTGGCGCC

22201 CGTCATCGAA ACCGTGTACC TGCACACGCC CTTCTCGGCC GGCAACGCCA  
CGAGTAGCTT TGGCACATGG ACGCGTGGCG GAAGAGCCGG CCGTTGCGGT

22251 CAACATAAAG AAGCAAGCAA CATCAACAAC AGCTGCCGCC ATGGGCTCCA  
GTTGTATTTC TTCGTTCTGTT GTAGTTGTTG TCGACGGCGG TACCCGAGGT

22301 GTGAGCAGGA ACTGAAAGCC ATTGTCAAAG ATCTTGGTTG TGGGCCATAT  
CACTCGTCTT TGACTTTCGG TAACAGTTTC TAGAACCAAC ACCCGGTATA

22351 TTTTGGGCA CCTATGACAA GCGCTTTCCA GGCTTTGTTT CTCCACACAA  
AAAAACCCGT GGATACTGTT CGCGAAAGGT CCGAAACAAA GAGGTGTGTT

22401 GCTCGCCTGC GCCATAGTCA ATACGGCCGG TCGCGAGACT GGGGGCGTAC  
CGAGCGGACG CGGTATCAST TATGCCGGCC AGCGCTCTGA CCCCCGATG

22451 ACTGGATGGC CTTTGCCTGG AACCCGCACT CAAAAACATG CTACCTCTTT  
TGACCTACCG GAAACGGACC TTGGGCGTGA GTTTTGTAC GATGGAGAAA

22501 GAGCCCTTTG GCTTTTCTGA CCAGCGACTC AAGCAGGTTT ACCAGTTTGA  
CTCGGGAAAC CGAAAAGACT GGTGCTGAG TTCGTCCAA TGGTCAAAT

22551 GTACGAGTCA CTCCTGCGCC GTAGCGCCAT TGCTTCTTCC CCCGACCGCT  
CATGCTCAGT GAGGACGCGG CATCGCGGTA ACGAAGAAGG GGGCTGGCGA

22601 GTATAACGCT GGAAGTCC ACCCAAAGCG TACAGGGGCC CAACTCGGCC  
CATATTGCGA CCTTTTCAGG TGGGTTTCGC ATGTCCCCGG GTTGAGCCGG

22651 GCCTGTGGAC TATTCTGCTG CATGTTTCTC CACGCCTTTG CCAACTGGCC  
CGGACACCTG ATAAGACGAC GTACAAAGAG GTGCGGAAAC GGTGACCGG

22701 CCAAACCTCC ATGGATCACA ACCCCACCAT GAACCTTATT ACCGGGGTAC  
GGTTTGAGGG TACCTAGTGT TGGGGTGGTA CTTGGAATAA TGCCCCCATG

Figure 26 X

22751 CCAACTCCAT GCTCAACAGT CCCAGGTAC AGCCACCGAT GGTTCGAC  
 GGTTCGAGTA CTTGTCA GGGGTCCATG TCGGGTGGGA CGCAGC  
 22801 CAGGAACAGC TCTACAGCTT CCTGGAGCGC CACTCGCCCT ACTTCCGCAG  
 GTCCTTGTGC AGATGTCGAA GGACCTCGCG GTGAGCGGGA TGAAGGCGTC  
 22851 CCACAGTGGC CAGATTAGGA GCGCCACTTC TTTTGTGTCAC TTGAAAAACA  
 GGTGTCACGC GTCTAATCCT CGCGGTGAAG AAAACAGTG AACTTTTGT  
 22901 TGTAATAATA ATGTACTAGA GACACTTTCA ATAAAGGCAA ATGCTTTTAT  
 ACATTTTAT TACATGATCT CTGTGAAAGT TATTTCCGTT TACGAAAAATA  
 22951 TTGTACACTC TCGGGTGATT ATTTACCCCC ACCCTTGCCG TCTGCGCCGT  
 AACATGTGAG AGCCCACTAA TAAATGGGGG TGGGAACGGC AGACGCGGCA  
 23001 TTAAAAATCA AAGGGGTCTT GCCGCGCATC GCTATGCGCC ACTGGCAGGG  
 AATTTTGTAGT TTCCCAAGA CGGCGCGTAG CGATACGCGG TGACCGTCCC  
 23051 ACACGTTGCG ATACTGGTGT TTAGTGCTCC ACTTAACTC AGGCACAACC  
 TGTGCAACGC TATGACCACA AATCAGGAGG TGAATTTGAG TCCGTGTTGG  
 23101 ATCCGCGGCA GCTCGGTGAA GTTTTCACTC CACAGGCTGC GCACCATCAC  
 TAGGCGCCGT CGAGCCACTT CAAAAGTGAG GTGTCCGACG CGTGGTAGTG  
 23151 CAACGCGTTT AGCAGGTGCG GCGCCGATAT CTGAAGTCC CAGTTGGGGC  
 GTTGCGCAAA TCGTCCAGCC CGCGGTATA GAACTTCAGC GTCAACCCCG  
 23201 CTCCGCCCTG CGCGCGCGAG TTGCGATACA CAGGGTTGCA GCACTGGAAC  
 GAGGCGGGAC CGCGCGGCTC AACGCTATGT GTCCCAACGT CGTGACCTTG  
 23251 ACTATCAGCG CCGGGTGGTG CACGCTGGCC AGCAGCTCT TGTGGAGAT  
 TGATAGTCGC GGCCACCAC GTGCGACCGG TCGTGGGAGA ACAGCCTCTA  
 23301 CAGATCCGCG TCCAGGTCTT CCGCGTTGCT CAGGGCGAAC GGAGTCAACT  
 GTCTAGGCGC AGGTCCAGGA GGCGCAACGA GTCCCGCTTG CCTCAGTTGA  
 23351 TTGGTAGCTG CCTTCCCAA AAGGGCGCGT GCCCAGGCTT TGAGTTGCAC  
 AACCATCGAC GGAAGGGTTT TTCCCGCGCA CGGGTCCGAA ACTCAACGTG  
 23401 TCGCACCGTA GTGGCATCAA AAGGTGACCG TGCCCGGTCT GGGCGTTAGG  
 AGCGTGGCAT CACCGTAGTT TTCCACTGGC ACGGGCCAGA CCGCAATCC  
 23451 ATACAGCGCC TGCATAAAG CCTTGATCTG CTTAAAGCC ACCTGAGCCT  
 TATGTCGCGG ACGTATTTTC GGAACAGAC GAATTTTCGG TGGACTCGGA  
 23501 TTGCGCCTTC AGAGAAGAAC ATGCGGCAAG ACTTGCCGGA AACTGATTG  
 AACCGGAAG TCTCTTCTTG TACGGCGTTC TGAACGGCCT TTTGACTAAC  
 23551 GCGGGACAGG CCGCGTCGTG CACGCAGCAC CTTGCGTCGG TGTGGAGAT  
 CGGCTGTCC GCGCAGCAC GTGCGTCGTG GAACGCAGCC ACAACCTCTA  
 23601 CTGCACCACA TTTGGGCCCC ACCGGTTCTT CACGATCTTG GCCTTGCTAG  
 GACGTGCTGT AAAGCCGGGG TGCCCAAGAA GTGCTAGAAC CGGAACGATC  
 23651 ACTGCTCCTT CAGCGCGCGC TGCCCGTTTT CGCTCGTCAC ATCCATTTC  
 TGACGAGGAA GTCGCGCGCG ACGGGCAAAA GCGAGCAGTG TAGGTAAAGT

Figure 26Y

23701 ATCACGTGCT CTTATTAT CATAATGCTT CCGTGTAGAC ACTTAATC  
TAGTGACACGA GGAATAAATA GTATTACGAA GGCACATCTG TGAATTCGAG

23751 GCCTTCGATC TCAGCGCAGC GGTGCAGCCA CAACGCGCAG CCCGTGGGCT  
CGGAAGCTAG AGTCGCGTCG CCACGTCGGT GTTGC GCGTC GGGCACCCGA

23801 CGTGATGCTT GTAGGTCACC TCTGCAAACG ACTGCAGGTA CGCCTGCAGG  
GCACTACGAA CATCCAGTGG AGACGTTTGC TGACGTCCAT GCGGACGTCC

23851 AATCGCCCCA TCATCGTCAC AAAGGTCTTG TTGCTGGTGA AGGTCAGCTG  
TTAGCGGGGT AGTAGCAGTG TTTCCAGAAC AACGACCACT TCCAGTCGAC

23901 CAACCCGCGG TGCTCCTCGT TCAGCCAGGT CTTCATACG GCCGCCAGAG  
GTTGGGCGCC ACGAGGAGCA AGTCGGTCCA GAACGTATGC CGGCGGTCTC

23951 CTTCCACTTG GTCAGGCAGT AGTTTGAAGT TCGCCTTTAG ATCGTTATCC  
GAAGGTGAAC CAGTCCGTCA TCAAACCTCA AGCGGAAATC TAGCAATAGG

24001 ACGTGGTACT TGTCCATCAG CGCGCGCGCA GCCTCCATGC CCTTCTCCCA  
TGCACCATGA ACAGGTAGTC GCGCGCGCGT CGGAGGTACG GGAAGAGGGT

24051 CGCAGACACG ATCGGCACAC TCAGCGGGTT CATCACCGTA ATTCACTTT  
GCGTCTGTGC TAGCCGTGTG AGTCGCCCCA GTAGTGGCAT TAAAGTGAAG

24101 CCGCTTCGCT GGGCTCTTCC TCTTCTCTT GCGTCCGCAT ACCACGCGCC  
GGCGAAGCGA CCCGAGAAGG AGAAGGAGAA CGCAGGCGTA TGGTGCGCGG

24151 ACTGGGTCGT CTTCATTGAG CCGCCGCACT GTGCGCTTAC CTCCTTTGCC  
TGACCCAGCA GAAGTAAGTC GCGGCGGTGA CACGCGAATG GAGGAAACGG

24201 ATGCTTGATT AGCACCGGTG GGTGCTGAA ACCCACCATT TGTAGCGCCA  
TAGCAACTAA TCGTGGCCAC CCAACGACTT TGGGTGGTAA ACATCGCGGT

24251 CATCTTCTCT TTCTTCCTCG CTGTCCACGA TTACCTCTGG TGATGGCGGG  
GTAGAAGAGA AAGAAGGAGC GACAGGTGCT AATGGAGACC ACTACCGCCC

24301 CGCTCGGGCT TGGGAGAAGG GCGCTCTTT TTCTTCTTGG GCGCAATGGC  
GCGAGCCCGA ACCCTCTTCC CGCGAAGAAA AAGAAGAACC CGCGTTACCG

24351 CAAATCCGCC GCCGAGGTG ATGGCCGCGG GCTGGGTGTG CGCGGCACCA  
GTTTAGGCGG CGGCTCCAGC TACCGGCGCC CGACCCACAC GCGCGGTGGT

24401 GCGCGTCTTG TGATGAGTCT TCCTCGTCCT CGGACTCGAT ACGCCGCCTC  
CGCGCAGAAC ACTACTCAGA AGGAGCAGGA GCCTGAGCTA TCGGCGGGAG

24451 ATCCGCTTTT TTGGGGGCGC CCGGGGAGGC GCGGCGGACG GGGACGGGGA  
TAGGCGAAAA AACCCCCGCG GGGCCCTCCG CCGCCGCTGC CCCTGCCCTT

24501 CGACACGTCC TCCATGGTTG GGGGACGTG CGCGGCACCG CGTCCGCGCT  
GCTGTGCAGG AGGTACCAAC CCCCTGCAGC GCGGCGTGGC GCAGGCGCGA

24551 CGGGGGTGGT TTCGCGCTGC TCCTCTTCCC GACTGGCCAT TTCCTTCTCC  
GCCCCACCA AAGCGCGACG AGGAGAAGGG CTGACCGGTA AAGGAAGAGG

24601 TATAGGCAGA AAAAGATCAT GGAGTCAGTC GAGAAGAAGG ACAGCCTAAC  
ATATCCGTCT TTTTCTAGTA CCTCAGTCAG CTCTTCTTCC TGTGCGATTG

Figure 262

24651 CGCCCCCTCT GTCGCCA CCACCGCCTC CACCGATGCC GCUAAGTC  
GCGGGGGAGA CTCAGCGGT GGTGGCGGAG GTGGCTACGG CGGTTGCCCG

24701 CTACCACCTT CCCCCTCGAG GCACCCCGC TTGAGGAGGA GGAAGTGATT  
GATGGTGGAA GGGGCAGCTC CGTGGGGCG AACTCCTCCT CCTTCACTAA

24751 ATCGAGCAGG ACCCAGGTTT TGTAAAGCAA GACGACGAGG ACCGCTCAGT  
TAGCTCGTCC TGGGTCCAAA ACATTGCTT CTGCTGCTCC TGGCGAGTCA

24801 ACCAACAGAG GATAAAAAGC AAGACCAGGA CAACGCAGAG GCAAACGAGG  
TGGTTGTCTC CTATTTTTCG TTCTGGTCCT GTGCGTCTC CGTTTGCTCC

24851 AACAAAGTCGG GCGGGGGGAC GAAAGGCATG GCGACTACCT AGATGTGGGA  
TTGTTACGCC CGCCCCCTG CTTTCGTAC CGCTGATGGA TCTACACCTT

24901 GACGACGTGC TGTGAAGCA TCTGCAGCGC CAGTGCGCCA TTATCTGCGA  
CTGCTGCAGG ACAACTTCGT AGACGTGCGG GTCACGCGGT AATAGACGCT

24951 CGCGTTGCAA GAGCGCAGCG ATGTGCCCT CGCCATAGCG GATGTCAGCC  
GCGCAACGTT CTCGCGTCGC TACACGGGGA GCGGTATCGC CTACAGTCGG

25001 TTGCCTACGA ACGCCACCTA TTCTCACCGC GCGTACCCCG CAAACGCCAA  
AACGGATGCT TCGGCTGGAT AAGAGTGGCG CGCATGGGG GTTTGCGGTT

25051 GAAAACGGCA CATGCGAGCC CAACCCGCGC CTCAACTTCT ACCCCGTATT  
CTTTTGCCGT GTACGCTCGG GTTGGGCGCG GAGTTGAAGA TGGGGCATAA

25101 TGCCGTGCCA GAGGTGCTTG CCACCTATCA CATCTTTTTC CAAACTGCA  
ACGGCACGGT CTCCACGAAC GGTGGATAGT GTAGAAAAAG GTTTTGACGT

25151 AGATACCCCT ATCCTGCCGT GCCAACCACA GCGGAGCGGA CAAGCAGCTG  
TCTATGGGGA TAGGACGGCA CGGTTGGCGT CGGCTCGCT GTTCGTCGAC

25201 GCCTTGCGGC AGGGCGCTGT CATACTGAT ATCGCCTCGC TCAACGAAGT  
CGGAACGCCG TCCGCGACA GTATGGACTA TAGCGGAGCG AGTTGCTTCA

25251 GCCAAAAATC TTTGAGGGTC TTGGACGCGA CGAGAAGCGC GCGGCAAACG  
CGGTTPTTAG AAACTCCAG AACCTGCCT GCTCTTCGCG CGCCGTTTGC

25301 CTCTGCAACA GGAAAACAGC GAAAATGAAA GTCACCTCTGG AGTGTGGTG  
GAGACGTTGT CTTTTGTGCG CTTTACTTT CAGTGAGACC TCACAACCAC

25351 GAACTCGAGG GTGACAACGC GCGCCTAGCC GTACTAAAAC GCAGCATCGA  
CTTGAGCTCC CACTGTTGCG CGCGGATCGG CATGATTTTG CGTCGTAGCT

25401 GGTCACCAC TTTGCCTACC CGGCACTTAA CCTACCCCGG AAGGTCATGA  
CCAGTGGGTG AAACGGATGG GCCGTGAATT GGATGGGGGG TTCCAGTACT

25451 GCACAGTCAT GAGTGAGCTG ATCGTGCGCC GTGCGCAGCC CCTGGAGAGG  
CGTGTAGTA CTCACGAC TAGCACGCGG CACGCGTCGG GGACCTCTCC

25501 GATGCAAATT TGCAAGACA AACAGAGGAG GGCCTACCG CAGTTGGCGA  
CTACGTTTAA ACGTTCTGT TTGTCTCCTC CCGGATGGGC GTCAACCGCT

25551 CGAGCAGCTA GCGCGCTGGC TTCAAACGCG CGAGCCTGCC GACTTGAGG  
GCTCGTCGAT CGCGCGACCG AAGTTTGGCG GCTCGGACCG CTGAACCTCC

Figure 26 AA

25601 AGCGACGCAA AATGATG GCCGCACTGC TCGTTACCGT GGAGCTAG  
TCGCTGCGTT TGATTACTAC CGGCGTCACG AGCAATGGCA CCTCGAACTC

25651 TGCATGCAGC GGTCTTTTGC TGACCCGGAG ATGCAGCGCA AGCTAGAGGA  
ACGTACGTCG CCAAGAAACG ACTGGGCCTC TACGTGCGCT TCGATCTCCT

25701 AACATTGCAC TACACCTTTC GACAGGGCTA CGTACGCCAG GCCTGCAAGA  
TTGTAACGTG ATGTGGAAG CTGTCCCGAT GCATCGCGTC CGGACGTTCT

25751 TCTCCAACGT GGAGCTCTGC AACCTGGTCT CCTACCTTGG AATTTTGCAC  
AGAGGTTGCA CCTCGAGACG TTGGACCAGA GGATGGAACC TTAAACGTG

25801 GAAAACCGCC TTGGGCAAAA CGTGCTTCAT TCCACGCTCA AGGGCGAGGC  
CTTTTGGCGG AACCCGTTTT GCACGAAGTA AGGTGCGAGT TCCCGCTCCG

25851 GCGCCGCGAC TACGTCCGCG ACTGCGTTTA CTTATTTCTA TGCTACACCT  
CGCGGCGCTG ATGCAGGCGC TGACGCAAAT GAATAAGAT ACGATGTGGA

25901 GGCAGACGGC CATGGGCGTT TGGCAGCAGT GCTTGGAGGA GTGCAACCTC  
CCGTCTGCCG GTACCCGCAA ACCGTGCTCA CGAACCTCCT CACGTGGAG

25951 AAGGAGCTGC AGAACTGCT AAAGCAAAAC TTGAAGGACC TATGGACGGC  
TTCTTCGACG TCTTTGACGA TTTGTTTTG AACTTCCTGG ATACCTGCCG

26001 CTTCAACGAG CGCTCCGTGG CCGCGCACCT GCGGACATC ATTTTCCCG  
GAAGTTGCTC GCGAGGCACC GCGCGGTGGA CCGCTGTAG TAAAAGGGG

26051 AACGCCTGCT TAAAACCTG CAACAGGCTC TGCCAGACTT CACCAGTCAA  
TTGCGGACGA ATTTTGGGAC GTTGTCCTAG ACGGTCTGAA GTGGTCAGTT

26101 AGCATGTTGC AGAACTTTAG GAACTTTATC CTAGAGCGCT CAGGAATCTT  
TCGTACAACG TCTTGAAATC CTTGAAATAG GATCTCGCGA GTCCTTAGAA

26151 GCGCGCCACC TGCTGTGCAC TTCCTAGCGA CTTTGTGCC ATTAAGTACC  
CGGGCGGTGG ACGACACGTG AAGGATCGCT GAAACACGGG TAATTCATGG

26201 GCGAATGCCC TCCGCCGCTT TGGGGCCACT GCTACCTTCT GCAGCTAGCC  
CGCTTACGGG AGGCGGCGAA ACCCCGGTGA CGATGGAAGA CGTCGATCGG

26251 AACTACCTTG CCTACCACTC TGACATAATG GAAGACGTGA GCGGTGACGG  
TTGATGGAAC GGATGGTGAG ACTGTATTAC CTTCTGCACT CGCCACTGCC

26301 TCTACTGGAG TGTCACCTGC GCTGCAACCT ATGCACCCCG CACCGCTCCC  
AGATGACCTC ACAGTGACAG CGACGTTGGA TACGTGGGGC GTGGCGAGGG

26351 TGGTTTGCAA TTCGAGCTG CTTAACGAAA GTCAAATTAT CGGTACCTTT  
ACCAAACGTT AAGCGTCGAC GAATTGCTTT CAGTTTAATA GCCATGGAAA

26401 GAGCTGCAGG GTCCCTCGCC TGACGAAAAG TCCGCGGCTC CGGGGTTGAA  
CTCGACGTCC CAGGGAGCGG ACTGCTTTTC AGGCGCCGAG GCCCAACTT

26451 ACTCACTCCG GGGCTGTGGA CGTCGGCTTA CCTTCGCAA TTTGTACCTG  
TGAGTGAGGC CCCGACACCT GCAGCCGAAT GGAAGCGTTT AAACATGGAC

26501 AGGACTACCA CGCCACGAG ATTAGTTCT ACGAAGACCA ATCCCGCCCC  
TCTGATGGT GCGGGTGCTC TAATCCAAGA TGCTTCTGGT TAGGGCGGGC

Figure 26 AB

26551 CCTAATGCGG AATATACCGC CTGCGTCATT ACCCAGGGCC ACATTCTGG  
 GGATTACGCC TCGAATGGCG GACGCAGTAA TGGGTCCCGG TGTAAAGAACC  
 26601 CCAATTGCAA GCCATCAACA AAGCCCGCCA AGAGTTTCTG CTACGAAAGG  
 GGTTAACGTT CGGTAGTTGT TTCGGGCGGT TCTCAAAGAC GATGCTTTCC  
 26651 GACGGGGGGT TTACTTGGAC CCCAGTCCG GCGAGGAGCT CAACCCAATC  
 CTGCCCCCA AATGAACCTG GGGGTCAGGC CGTCTCTCGA GTTGGGTTAG  
 26701 CCCCCGCGC CGCAGCCCTA TCAGCAGCAG CCGCGGGCCC TTGCTTCCCA  
 GGGGGCGCGG GCGTCGGGAT AGTCGTCGTC GGCGCCCGGS AACGAAGGGT  
 26751 GGATGGCACC CAAAAGAAG CTGCAGCTGC CGCCGCCACC CACGGACGAG  
 CCTACCGTGG GTTTTCTTTC GACGTCGACG GCGGCGGTGG GTGCCTGCTC  
 26801 GAGGAATACT GGGACAGTCA GGCAGAGGAG GTTTTGGACG AGGAGGAGGA  
 CTCCTTATGA CCTGTCAGT CCGTCTCCTC CAAAACCTGC TCCTCTCCT  
 26851 GGACATGATG GAAGACTGGG AGAGCCTAGA CGAGGAAGCT TCCGAGGTCTG  
 CCTGTACTAC CTTCGACCC TCTCGGATCT GCTCCTTCGA AGGCTCCAGC  
 26901 AAGAGGTGTC AGACGAAACA CCGTCACCCT CGGTGCAATT CCCCTCGCCG  
 TTCTCCACAG TCTGCTTTGT GGCAGTGGGA GCCAGCGTAA GGGGAGCGGC  
 26951 GCGCCCCAGA AATCGGCAAC CGGTTCAGC ATGGCTACAA CCTCCGCTCC  
 CGCGGGGTCT TTAGCCGTG GCCAAGGTCTG TACCGATGTT GGAGGCGAGG  
 27001 TCAGGCGCGC CCGCACTGC CCGTTCGCGG ACCCAACCGT AGATGGGACA  
 AGTCCGCGGC GGCCGTGACG GGCAAGCGGC TGGGTTGGCA TCTACCTGT  
 27051 CCACTGGAAC CAGGGCCGGT AAGTCCAAGC AGCCGCCCGC GTTAGCCCAA  
 GGTGACCTTG GTCCCGGCCA TTCAGGTTCTG TCGGCGCGCG CAATCGGGTT  
 27101 GAGCAACAAC AGCGCCAAGG CTACCGCTCA TGGCGCGGGC ACAAGAACGC  
 CTCGTTGTTG TCGCGGTTC GATGGCGAGT ACCGCGCCCG GTTCTTTGCG  
 27151 CATAGTTGCT TGCTTGCAAG ACTGTGGGGG CAACATCTCC TTCGCCCGCC  
 GTATCAACGA ACGAACGTTG TGACACCCCC GTTGTAGAGG AAGCGGGCGG  
 27201 GCTTTCTTCT CTACCATCAC GGCCTGGCCT TCCCCGTAA CATCCTGCAT  
 CGAAAGAAGA GATGGTAGTG CCGCACCGGA AGGGGGCATT GTAGGACGTA  
 27251 TACTACCGTC ATCTCTACAG CCCATACTGC ACCGGCGGCA GCGGCAGCAA  
 ATGATGGCAG TAGAGATGTC GGGTATGACG TGGCCGCCGT CGCCGTCGTT  
 27301 CAGCAGCGGC CACACAGAAG CAAAGGCGAC CGGATAGCAA GACTCTGACA  
 GTCGTGCGCG GTGTGCTTC GTTCCGCTG GCCTATCGTT CTGAGACTGT  
 27351 AAGCCCAAGA AATCCACAGC GCGGCGAGCA GCAGGAGGAG GAGCGCTGCG  
 TTCGGGTCTT TTAGGTGTCG CCGCCGTCGT CGTCTCTCTC CTCGCGACGC  
 27401 TCTGGCGCCC AACGAACCCG TATCGACCCG CGAGCTTAGA AACAGGATTT  
 AGACCGCGGG TTGCTTGGGC ATAGCTGGGC GCTCGAATCT TTGTCTAAA  
 27451 TTCCCACTCT GTATGCTATA TTTCAACAGA GCAGGGGCCA AGAACAAGAG  
 AAGGGTGAGA CATACGATAT AAAGTTGTCT CGTCCCGGT TCTTGTCTC

Figure 26 AC

27501 CTGAAAATAA A CAGGTC TCTGCGATCC CTCACCCGCA GCTGCC TA  
 GACTTTTATT TTTGTCCAG AGACGCTAGG GAGTGGGCGT CGACGGACAT  
 27551 TCACAAAAGC GAAGATCAGC TTCGGCGCAC GCTGGAAGAC GCGGAGGCTC  
 AGTGTTTTCG CTCTAGTCG AAGCCGCGTG CGACCTTCTG CGCCTCCGAG  
 27601 TCTTCAGTAA ATACTGCGCG CTGACTCTTA AGGACTAGTT TCGCGCCCTT  
 AGAAGTCATT TATGACGCGC GACTGAGAAT TCCTGATCAA AGCGCGGGAA  
 27651 TCTCAAATTT AAGCGCGAAA ACTACGTCAT CTCCAGCGGC CACACCCGGC  
 AGAGTTTAAA TTCGCGCTTT TGATGCAGTA GAGGTCGCCG GTGTGGGCCG  
 27701 GCCAGCACCT GTTGTACGCG CCATTATGAG CAAGGAAATT CCCACGCCCT  
 CGGTCGTGGA CAACAGTCGC GGTAAIATC GTTCCTTTAA GGGTCCGGGA  
 27751 ACATGTGGAG TTACCAGCCA CAAATGGGAC TTGCGGCTGG AGCTGCCCAA  
 TGTACACCTC AATGGTCGGT GTTACCTG AACGCCGACC TCGACGGGT  
 27801 GACTACTCAA CCCGAATAAA CTACATGAGC GCGGGACCCC ACATGATATC  
 CTGATGAGTT GGGCTTATTT GATGTACTCG CGCCCTGGGG TGTACTATAG  
 27851 CCGGGTCAAC GGAATACGCG CCCACCGAAA CCGAATTCTC CTGGAACAGG  
 GGCCCACTTG CTTATGCGC GGGTGGCTTT GGCTTAAGAG GACCTTGTCC  
 27901 CGGCTATTAC CACCACACCT CGTAATAACC TTAATCCCCG TAGTTGGCCC  
 GCCGATAATG GTGGTGTGGA GCATTATTGG AATTAGGGGC ATCAACCGGG  
 27951 GCTGCCCTGG TGTACCAGGA AAGTCCCGCT CCCACCACTG TGGTACTTCC  
 CGACGGGACC ACATGGTCTT TTCAGGGCGA GGGTGGTGAC ACCATGAAGG  
 28001 CAGAGACGCC CAGSCCGAAG TTCAGATGAC TAACTCAGGG GCGCAGCTTG  
 GTCTCTGCGG GTCCGGCTTC AAGTCTACTG ATTGAGTCCC CGCGTCAAC  
 28051 CCGGCGGCTT TCGTCACAGG GTGCGGTCCG CCGGCGAGGG TATAACTCAC  
 GCGCGCCGAA AGCAGTGTCC CACGCCAGCG GGCCCGTCCC ATATTGAGTG  
 28101 CTGACAATCA GAGGGCGAGG TATTCAGCTC AACGACGAGT CGGTGAGCTC  
 GACTGTTAGT CTCCCGCTCC ATAAGTCGAG TTGCTGCTCA GCCACTCGAG  
 28151 CTCGCTTGGT CTCCGTCCCG ACGGGACATT TCAGATCGGC GCGCGCGGCC  
 GAGCGAACCA GAGGCAGGCC TGCCCTGTAA AGTCTAGCCG CCGCGGCCGG  
 28201 GCTCTTCATT CACGCCCTCGT CAGGCAATCC TAACTCTGCA GACCTCGTCC  
 CGAGAAGTAA GTGCGGAGCA GTCCGTTAGG ATTGAGACGT CTGGAGCAGG  
 28251 TCTGAGCCGC GCTCTGGAGG CATTGGAAT CTGCAATTTA TTGAGGAGTT  
 AGACTCGGCG CGAGACCTCC GTAACCTTGA GACGTAAAT AACTCCTCAA  
 28301 TGTGCCATCG GTCTACTTTA ACCCCTTCTC GGGACCTCCC GGCCACTATC  
 ACACGGTAGC CAGATGAAAT TGGGGAAGAG CCCTGGAGGG CCGGTGATAG  
 28351 CGGATCAATT TATTCCTAAC TTTGACGCGG TAAAGGACTC GCGGACGGC  
 GCCTAGTTAA ATAAGGATTG AACTGCGCC ATTCCTGAG CCGCCTGCCG  
 28401 TACGACTGAA TGTAAAGTGG AGAGGCAGAG CAACTGCGCC TGAAACACCT  
 ATGCTGACTT ACAATTCACC TCTCCGTCTC GTTGACGCGG ACTTTGTGGA

Figure 26 AD

28451 GGTCCACTGT CCGCGCCACA AGTGCTTTGC CCGCGACTCC GGTGAGTTT  
 CCAGGTGACA GCGGCGGTGT TCACGAAACG GGCCTGAGG CCACTCAAAA  
 28501 GCTACTTTGA ATTGCCCAG AGTCATATCG AGGGCCCGGC GCACGGCGTC  
 CGATGAAACT TAACGGGCTC CTAGTATAGC TCCCGGGCCG CGTGCCGCAG  
 28551 CGGCTTACCG CCCAGGGAGA GCTTGCCCGT AGCCTGATTG GGGAGTTTAC  
 GCCGAATGGC GGGTCCCTCT CGAACGGGCA TCGGACTAAG CCCTCAAATG  
 28601 CCAGCGCCCC CTGCTAGTTG AGCGGGACAG GGGACCCTGT GTTCTCACTG  
 GGTGCGGGG GACGATCAAC TCGCCCTGTC CCCTGGGACA CAAGAGTGAC  
 28651 TGATTTGCAA CTGTCCTAAC CCTGGATTAC ATCAAGATCT TTGTTGCCAT  
 ACTAAACGTT GACAGGATTG GGACCTAATG TAGTTCTAGA AACAACGGTA  
 28701 CTCTGTGCTG AGTATAATAA ATACAGAAAT TAAATATAC TGGGGCTCCT  
 GAGACACGAC TCATATTATT TATGTCTTTA ATTTTATATG ACCCCGAGGA  
 28751 ATCGCCATCC TGTAACGCC ACCGTCTTCA CCCGCCCCAAG CAAACCAAGG  
 TAGCGGTAGG ACATTTGCGG TGGCAGAAGT GGGCGGGTTC GTTTGGTTCC  
 28801 CGAACCTTAC CTGCTACTTT TAACATCTCT CCCTCTGTGA TTTACAACAG  
 GCTTGGAATG GACCATGAAA ATTGTAGAGA GGGAGACACT AAATGTTGTC  
 28851 TTCAACCCA GACGGAGTGA GTCTACGAGA GAACCTCTCC GAGCTCAGCT  
 AAAGTTGGGT CTGCTCACT CAGATGCTCT CTTGGAGAGG CTCGAGTCGA  
 28901 ACTCCATCAG AAAAAACACC ACCCTCCTTA CCTGCCGGA ACGTACGAGT  
 TGAGGTAGTC TTTTGTGG TGGGAGGAAT GGACGGCCCT TGCATGCTCA  
 28951 GCGTCACCGG CCGCTGCACC ACACCTACCG CCTGACCGTA AACCAGACTT  
 CGCAGTGGCC GCGGACGTGG TGTGGATGGC GGACTGGCAT TTGGTCTGAA  
 29001 TTTCGGACA GACCTCAATA ACTCTGTTTA CCAGAACAGG AGGTGAGCTT  
 AAAGGCCTGT CTGGAGTTAT TGAGACAAAT GGTCTTGTC TCCACTCGAA  
 29051 AGAAAACCTT CAGGGTATTA GGCCAAAGGC GCAGCTACTG TGGGGTTTAT  
 TCTTTTGGGA ATCCATAAT CCGGTTTCCG CGTCGATGAC ACCCCAAATA  
 29101 GAACAATCA AGCAACTCTA CCGGCTATTC TAATTCAGGT TTCTCTAGAA  
 CTGTTAAGT TCGTTGAGAT GCCCATAAG ATTAAGTCCA AAGAGATCTT  
 29151 TCGGGGTGG GGTATTCTC TGTCTGTGA TTCTCTTTAT TCTTATACTA  
 AGCCCCAACC CCAATAAGAG ACAGAACACT AAGAGAAATA AGAATATGAT  
 29201 ACGCTTCTCT GCCTAAGGCT CGCCGCTGTC TGTGTGCACA TTGCAATTTA  
 TGCGAAGAGA CGGATTCCGA GCGGCGGACG ACACACGTGT AAACGTAAAT  
 29251 TTGTCAGCTT TTTAAACGCT GGGGTCGCCA CCCAAGATGA TTAGGTACAT  
 AACAGTCGAA AAATTTGCGA CCCCAGCGGT GGGTTCTACT AATCCATGTA  
 29301 AATCCTAGGT TTAATCACCC TTGCGTCAGC CCACGGTACC ACCCAAAGG  
 TTAGGATCCA AATGAGTGGG AACGCAGTCG GGTGCCATGG TGGGTTTCC  
 29351 TGGATTTTAA GGAGCCAGCC TGTAAATGTTA CATTCGCAGC TGAAGCTAAT  
 ACCTAAATTT CTTGGTTCGG ACATTACAAT GTAAGCGTCG ACTTCGATTA

Figure 26 AE

29401 GAGTGCACCA CTTATAAA ATGCACCACA GAACATGAAA AGCTGUAAT  
 CTCACGTGGT GAGAATATTT TACGTGGTGT CTTGTACTTT TCGACGAATA  
 29451 TCGCCACAAA AACAAAATG GCAAGTATGC TGTATTATGCT ATTTGGCAGC  
 AGCGGTGTTT TTGTTTTAAC CGTTCATACG ACAAATACGA TAAACCGTCG  
 29501 CAGGTGACAC TACAGAGTAT AATGTTACAG TTTTCCAGGG TAAAAGTCAT  
 GTCCACTGTG ATGTCTCATA TTACAATGTC AAAAGGTCCC ATTTTCAGTA  
 29551 AAAACTTTTA TGTATACTTT TCCATTTTAT GAAATGTGCG ACATTACCAT  
 TTTTGAAAAT ACATATGAAA AGGTAAAATA CTTTACACGC TGTATGGTA  
 29601 GTACATGAGC AAACAGTATA AGTTGTGGCC CCCACAAAAT TGTGTGGAAA  
 CATGTACTCG TTTGTCATAT TCAACACCGG GGGTGTTTTA ACACACCTTT  
 29651 ACACTGGCAC TTTCTGCTGC ACTGCTATGC TAATTACAGT GCTCGCTTTG  
 TGTGACCGTG AAAGACGACG TGACGATACG ATTAATGTCA CGAGCGAAAC  
 29701 GTCTGTACCC TACTCTATAT TAAATACAAA AGCAGACGCA GCTTTATTGA  
 CAGACATGGG ATGAGATATA ATTTATGTTT TCGTCTGCGT CGAAATAACT  
 29751 GGAAAAGAAA ATGCCTTAAT TTAATAAGTT ACAAAGCTAA TGTCAACCACT  
 CCTTTCTTT TACGGAATTA AATGATTCAA TGTTCGATT ACAGTGGTGA  
 29801 AACTGCTTTA CTCGCTGCTT GCAAAACAAA TTCAAAAAGT TAGCATTATA  
 TTGACGAAAT GAGCGACGAA CGTTTTGTTT AAGTTTTTCA ATCGTAATAT  
 29851 ATTAGAATAG GATTTAAACC CCCCGGTCAT TTCCTGCTCA ATACCATTCC  
 TAATCTTATC CTAAATTTGG GGGGCCAGTA AAGGACGAGT TATGGTAAGG  
 29901 CCTGAACAAT TGAATCTATG TGGGATATGC TCCAGCGCTA CAACCTTGAA  
 GGACTTGTTA ACTGAGATAC ACCCTATACG AGGTGCGGAT GTTGGAACTT  
 29951 GTCAGGCTTC CTGGATGTCA GCATCTGACT TTGGCCAGCA CCTGTCCCGC  
 CAGTCCGAAG GACCTACAGT CGTAGACTGA AACCAGTCGT GGACAGGGCG  
 30001 GGATTTGTTT CAGTCCAAT ACAGCGACCC ACCCTAACAG AGATGACCAA  
 CCTAAACAAG GTCAGGTTGA TGTGCTGGG TGGGATTGTC TCTACTGGTT  
 30051 CACAACCAAC GCGGCCGCGG CTACCGGACT TACATCTACC ACAAATACAC  
 GTGTTGGTTG CGCCGCGGCG GATGGCCTGA ATGTAGATGG TGTATTATGT  
 30101 CCCAAGTTTC TGCTTTGTC AATAACTGGG ATAACCTGGG CATGTGGTGG  
 GGGTTCAAAG ACGGAAACAG TTATTGACCC TATTGAACCC GTACACCACC  
 30151 TTCTCCATAG CGCTTATGTT TGTATGCCTT ATTATTATGT GGCTCATCTG  
 AAGAGGTATC GCGAATACAA ACATACGGAA TAATAATACA CCGAGTAGAC  
 30201 CTGCCTAAAG CGCAAACGCG CCCGACCACC CATCTATAGT CCCATCATTG  
 GACGGATTTC GCGTTGCGC GGGCTGGTGG GTAGATATCA GGGTAGTAAC  
 30251 TGCTACACCC AAACAATGAT GGAATCCATA GATTGGACGG ACTGAAACAC  
 ACGATGTGGG TTTGTTACTA CCTTAGGTAT CTAACCTGCC TGACTTTGTG  
 30301 ATGTTCTTTT CTCTTACAGT ATGATTAAAT GAGACATGAT TCCTCGAGTT  
 TACAAGAAAA GAGAATGTCA TACTAATTTA CTCTGTACTA AGGAGCTCAA

Figure 26 AF

30351 TTTATATTAC T CCTTGT TGGGCTTTT TGTGCGTGCT CCACAT C  
 AAATATAATG ACTGGGAACA ACGCGAAAAA ACACGCACGA GGTGTAACCG  
 30401 TGGCGTTTCT CACATCGAAG TAGACTGCAT TCCAGCCCTC ACAGTCTATT  
 ACGCCAAAGA GTGTAGCTTC ATCTGACGTA AGGTCGGAAG TGTCAGATAA  
 30451 TGCTTTACGG ATTTGTCACC CTCACGCTCA TCTGCAGCCT CATCACTGTG  
 ACGAAATGCC TAAACAGTGG GAGTGCAGT AGACGTCGGA GTAGTGACAC  
 30501 GTCATCGCCT TTATCCAGTG CATTGACTGG GTCTGTGTGC GCTTTGCATA  
 CAGTAGCGGA AATAGGTCAC GTAACGTACC CAGACACACG CGAAACGTAT  
 30551 TCTCAGACAC CATCCCCAGT ACAGGGACAG GACTATAGCT GAGCTTCTTA  
 AGAGTCTGTG GTAGGGGTCA TGTCCTGTCT CTGATATCGA CTCGAAGAAT  
 30601 GAATTCTTTA ATTATGAAAT TTACTGTGAC TTTTCTGCTG ATTATTTGCA  
 CTTAAGAAAT TAATACTTTA AATGACACTG AAAAGACGAC TAATAAACGT  
 30651 CCCTATCTGC GTTTTGTTC CCGACCTCCA AGCCTCAAAG ACATATATCA  
 GGGATAGACG CAAAACAAGG GGCTGGAGGT TCGGAGTTTC TGTATATAGT  
 30701 TGCAGATTCA CTCGTATATG GAATATTCCA AGTTGCTACA ATGAAAAAAG  
 ACGTCTAAGT GAGCATATAC CTTATAAGGT TCAACGATGT TACTTTTTTC  
 30751 CGATCTTTCC GAAGCCTGGT TATATGCAAT CATCTCTGTT ATGGTGTCTT  
 GCTAGAAAGG CTTCCGGACCA ATATACGTTA GTAGAGACAA TACCACAAGA  
 30801 GCAGTACCAT CTTAGCCCTA GCTATATATC CCTACCTTGA CATTTGGCTGG  
 CCTCATGGTA GAATCGGGAT CGATATATAG GGATGGAAC GTAAACGACC  
 30851 AACGCAATAG ATGCCATGAA CCACCCAACT TTCCCGCGCG CCGCTATGCT  
 TTGCGTTATC TACGGTACTT GGTGGGTTGA AAGGGGCGCG GCGGATACGA  
 30901 TCCACTGCAA CAAGTTGTTG CCGGCGGCTT TGTCCAGCC AATCAGCCTC  
 AGGTGACGTT GTTCAACAAC GGCCGCCGAA ACAGGGTCGG TTAGTCGGAG  
 30951 GCCCACCTTC TCCCACCCCT ACTGAAATCA GCTACTTTAA TCTAACAGGA  
 CGGGTGGAAG AGGGTGGGGG TGACTTTAGT CGATGAAAT AGATTGTCCT  
 31001 GGAGATGACT GACACCCTAG ATCTAGAAAT GGACGGAAT ATTACAGAGC  
 CCTCTACTGA CTGTGGGATC TAGATCTTTA CCTGCCTTAA TAATGTCTCG  
 31051 AGCGCCTGCT AGAAAGACGC AGGCGAGCGG CCGAGCAACA GCGCATGAAT  
 TCGCGGACGA TCTTTCTGCG TCCCGTCGCC GGCTCGTTGT CCGCTACTTA  
 31101 CAAGAGCTCC AAGACATGGT TAACTTGAC CAGTGCAAAA GGGGTATCTT  
 GTTCTCGAGG TTCTGTACCA ATTGAACGTG GTCACGTTTT CCCCATAGAA  
 31151 TTGTCTCGTA AAGCAGGCCA AAGTCACCTA CGACAGTAAT ACCACCGGAC  
 AACAGAGCAT TTCGTCCGGT TTCAGTGGAT GCTGTCATTA TGGTGGCCTG  
 31201 ACCGCCCTTAG CTACAAGTTG CCAACCAAGC GTCAGAAATT GGTGGTCATG  
 TGGCGGAATC GATGTTCAAC GGTGGGTTG CAGTCTTTAA CCACAGTAC  
 31251 GTGGGAGAAA AGCCCATTAC CATAACTCAG CACTCGGTAG AAACCGAAGG  
 CACCCCTCTT TCGGGTAATG GTATTGAGTC GTGAGCCATC TTTGGCTTCC

Figure 26 AG

31301 CTGCATTAC TCTTGTG AAGGACCTGA GGATCTCTGC ACCCTTCTA  
 GACGTAAGTG AGTGGAAACAG TTCCTGGACT CCTAGAGACG TGGGAATCAT

31351 AGACCCTGTG CGGTCTCAAA GATCTTATTC CCTTTAACTA ATAAAAAAA  
 TCTGGGACAC GCCAGAGTTT CTAGAATAAG GGAAATTGAT TATTTTITTT

31401 ATAATAAAGC ATCACTTACT TAAAATCAGT TAGCAAATTT CTGTCCAGTT  
 TATTATTTTCG TAGTGAATGA ATTTTAGTCA ATCGTTTAAA GACAGGTCAA

31451 TATTCAGCAG CACCTCCTTG CCCTCCTCCC AGCTCTGGTA TTGCAGCTTC  
 ATAAGTCGTC GTGGAGGAAC GGGAGGAGGG TCGAGACCAT AACGTCGAAG

31501 CTCCTGGCTG CAAACTTTCT CCACAATCTA AATGGAATGT CAGTTTCCTC  
 GAGGACCGAC GTTTGAAAGA GGTGTTAGAT TTACCTTACA GTCAAAGGAG

31551 CTGTTCTGT CCATCCGCAC CCACTATCTT CATGTTGTTG CAGATGAAGC  
 GACAAGGACA GGTAGGCGTG GGTGATAGAA GTACAACAAC GTCTACTTCG

31601 GCGCAAGACC GTCTGAAGAT ACCTTCAACC CCGTGTATCC ATATGACACG  
 CGCGTTCTGG CAGACTTCTA TGGAAAGTTGG GGCACATAGG TATACTGTGC

31651 GAAACCGGTC CTCCAACGTG GCCTTTTCTT ACTCCTCCCT TTGTATCCCC  
 CTTTGGCCAG GAGGTTGACA CGGAAAAGAA TGAGGAGGGA AACATAGGGG

31701 CAATGGGTTT CAAGAGAGTC CCCCTGGGGT ACTCTCTTTG CGCCTATCCG  
 GTTACCCAAA GTTCTCTCAG GGGGACCCCA TGAGAGAAAC GCGGATAGGC

31751 AACCTCTAGT TACCTCCAAT GGCATGCTTG CGCTCAAAAT GGGCAACGGC  
 TTGGAGATCA ATGGAGGTTA CCGTACGAAC GCGAGTTTA CCCGTTGCCG

31801 CTCTCTCTGG ACGAGGCCGG CAACCTTACC TCCCAAAATG TAACCACTGT  
 GAGAGAGACC TGCTCCGGCC GTTGGAAATGG AGGGTTTATC ATTGGTGACA

31851 GAGCCCACCT CTCAAAAAA CCAAGTCAAA CATAAACCTG GAAATATCTG  
 CTCGGGTGGA GAGTTTTTTT GGTTCAGTTT GTATTTGGAC CTTTATAGAC

31901 CACCCCTCAC AGTTACCTCA GAAGCCCTAA CTGTGGCTGC CGCCGCACCT  
 GTGGGGAGTG TCAATGGAGT CTTGGGGATT GACACCGACG GCGGCGTGGA

31951 CTAATGGTGC GGGGCAACAC ACTCACCATG CAATCACAGG CCCCCTAAC  
 GATTACCAGC GCCCGTTGTG TGAGTGGTAC GTTAGTGTCC GGGGCGATTG

32001 CGTGCACGAC TCCAACTTA GCATTGCCAC CCAAGGACCC CTCACAGTGT  
 GCACGTGCTG AGGTTTGAAT CGTAACGGTG GGTTCCTGGG GAGTGTGACA

32051 CAGAAGGAAA GCTAGCCCTG CAAACATCAG GCCCCCTCAC CACCACCGAT  
 GTCTTCCTTT CGATCGGGAC GTTTGTAGTC CGGGGGAGTG GTGGTGGCTA

32101 AGCAGTACCC TTAATATCAC TGCCCTACCC CCTCTAACTA CTGCCACTGG  
 TCGTCATGGG AATGATAGTG ACGGAGTGGG GGAGATTGAT GACGGTGACC

32151 TAGCTTGGGC ATTGACTTGA AAGAGCCCAT TTATACACAA AATGGAAAAC  
 ATCGAACCCG TAACTGAACT TTCTCGGGTA AATATGTGTT TTACCTTTTG

32201 TAGGACTAAA GTACGGGGCT CCTTTGCATG TAACAGACGA CCTAAACACT  
 ATCCTGATTT CATGCCCGA GGAAACGTAC ATTGTCTGCT GGATTGTGA

Figure 26 AH

32251 TTGACCGTAG CACTGGTCC AGGTGTGACT ATTAATAATA CTTCTTCTA  
 AACTGGCATC CAGACCAGG TCCACACTGA TAATTATTAT GAAGGAAGT  
 32301 AACTAAAGTT ACTGGAGCCT TGGGTTTTGA TTCACAAGGC AATATGCAAC  
 TTGATTTCAA TGACCTCGGA ACCCAAACT AAGTGTTCG TTATACGTTG  
 32351 TTAATGTAGC AGGAGGACTA AGGATTGATT CTCAAAACAG ACGCCTTATA  
 AATTACATCG TCCTCTGAT TCCTAACTAA GAGTTTGTG TCGGGAATAT  
 32401 CTTGATGTTA GTTATCCGTT TGATGCTCAA AACCAACTAA ATCTAAGACT  
 GAACTACAAT CAATAGGCAA ACTACGAGTT TTGGTTGATT TAGATTCTGA  
 32451 AGGACAGGGC CCTCTTTTAA TAACTCAGC CCACAACCTG GATATTAACCT  
 TCCTGTCCCG GGAGAAAAAT ATTTGAGTCG GGTGTTGAAC CTATAATTGA  
 32501 ACAACAAAGG CCTTTACTTG TTTACAGCTT CAAACAATTC CAAAAAGCTT  
 TGTGTTTCC GGAAATGAAC AAATGTCGAA GTTTGTTAAG GTTTTTTCGAA  
 32551 GAGGTTAACC TAAGCACTGC CAAGGGGTG ATGTTTGACG CTACAGCCAT  
 CTCAATTGG ATTCGTGACG GTTCCCAAC TACAACTGC GATGTCGGTA  
 32601 AGCCATTAAT GCAGGAGATG GGCTTGAATT TGGTTCACCT AATGCACCAA  
 TCGTAATTA CGTCTCTAC CCGAACTAA ACCAAGTGA TTACGTGGT  
 32651 ACACAAATCC CCTCAAACA AAAATTGGCC ATGGCCTAGA ATTTGATTCA  
 TGTGTTTAGG GGAGTTTGT TTTTAACCGG TACCGGATCT TAACTAAGT  
 32701 AACAAAGGCTA TGGTTCCTAA ACTAGGAAT GGCCTTAGTT TTGACAGCAC  
 TTGTCCGAT ACCAAGGATT TGATCCTGA CCGGAATCAA AACTGTCGTG  
 32751 AGGTGCCATT ACAGTAGGAA ACAAATAA TGATAAGCTA ACTTTGTGGA  
 TCCACGGTAA TGTCATCCTT TGTTTTATT ACTATTCGAT TGAACACCT  
 32801 CCACACCAGC TCCATCTCCT AACTGTAGAC TAAATGCAGA GAAAGATGCT  
 GGTGTGGTCG AGGTAGAGGA TTGACATCTG ATTTACGTCT CTTCTACGA  
 32851 AAATCACTT TGGTCTTAAC AAAATGTGGC AGTCAAATAC TTGCTACAGT  
 TTTGAGTGAA ACCAGAATTG TTTTACACCG TCAGTTTATG AACGATGTCA  
 32901 TTCAGTTTGG GCTGTTAAAG GCAGTTTGGC TCCAATATCT GGAACAGTTC  
 AAGTCAAAAC CGACAATTTT CGTCAACCG AGGTTATAGA CTTGTCAAG  
 32951 AAAGTGCTCA TCTTATTATA AGATTTGACG AAAATGGAGT GCTACTAAAC  
 TTTCACGAGT AGAATAATAT TCTAACTGC TTTTACCTCA CGATGATTG  
 33001 AATTCCTTCC TGGACCCAGA ATATTGGAAC TTTAGAAATG GAGATCTTAC  
 TTAAGGAAGG ACCTGGGTCT TATAACCTG AATCTTTAC CTCTAGAATG  
 33051 TGAAGGCACA GCCTATACAA ACGCTGTTGG ATTTATGCCT AACCTATCAG  
 ACTTCCGTGT CGGATATGTT TGCGACAACC TAAATACGGA TTGGATAGTC  
 33101 CTTATCCAAA ATCTCAGGT AAACTGCCA AAAGTAACAT TGTCAGTCAA  
 GAATAGGTTT TAGAGTGCCA TTTTGACGGT TTTTATTGTA ACAGTCAGTT  
 33151 GTTTACTTAA ACGGAGACAA AACTAAACCT GTAACACTAA CCATTACACT  
 CAAATGAATT TGCCTCTGTT TTGATTGGA CATTGTGAT GGTAAATGTGA

Figure 26 AI

33201 AAACGGTACA GAAACAG GAGACACAAC TCCAAGTGCA TACTCTTCT  
TTTGCCATGT GTCCTTTGTC CTCGTGTGTG AGGTTACAGT ATGAGATACA

33251 CATTTCATG GGACTGGTCT GGCCACAAC ACATTAATGA AATATTTGCC  
GTAAAAGTAC CCTGACCAGA CCGGTGTTGA TGTAAATTACT TTATAAACGG

33301 ACATCCTCTT ACACTTTTTC ATACATTGCC CAAGAATAAA GAATCGTTTG  
TGTAGGAGAA TGTGAAAAAG TATGTAACGG GTTCTTATTT CTTAGCAAAC

33351 TGTATGTTT CAACGTGTTT ATTTTCAAT TGCAGAAAAT TTCAAGTCAT  
ACAATACAAA GTTGACAAA TAAAAAGTTA ACGTCTTTTA AAGTTCAGTA

33401 TTTTCATTCA GTAGTATAGC CCCACCACCA CATAGCTTAT ACAGATCACC  
AAAAGTAAGT CATCATATCG GGGTGGTGGT GTATCGAATA TGTCTAGTGG

33451 GTACCTTAAT CAAACTCACA GAACCCTAGT ATTCAACCTG CCACCTCCCT  
CATGGAATTA GTTGAGTGT CTTGGGATCA TAAGTTGGAC GGTGGAGGGA

33501 CCCAACACAC AGAGTACACA GTCCTTTCTC CCCGGCTGGC CTTAAAAAGC  
GGGTTGTGTG TCTCATGTGT CAGGAAAGAG GGGCCGACCG GAATTTTTCG

33551 ATCATATCAT GGGTAACAGA CATATTCTTA GGTGTTATAT TCCACACGGT  
TAGTATAGTA CCCATTGTCT GTATAAGAAT CCACAATATA AGGTGTGCCA

33601 TTCCTGTGCA GCCAAACGCT CATCAGTGAT ATTAATAAAC TCCCCGGGCA  
AAGGACAGCT CGGTTTGC GAAGTCACTA TAATTATTG AGGGGCCCGT

33651 GCTCACTTAA GTTCATGTCG CTGTCCAGCT GCTGAGCCAC AGGCTGCTGT  
CGAGTGAATT CAAGTACAGC GACAGGTCGA CGACTCGGTG TCCGACGACA

33701 CCAACTTGGC GTTGCTTAAC GGGCGGCGAA GGAGAAGTCC ACGCCTACAT  
GGTTGAACGC CAACGAATTG CCCGCCGCTT CCTCTTCAGG TGCGGATGTA

33751 GGGGGTAGAG TCATAATCGT GCATCAGGAT AGGGCGGTGG TGCTGCAGCA  
CCCCATCTC AGTATTAGCA CGTAGTCCTA TCCCGCCACC ACGACGTCGT

33801 GCGCGCGAAT AAAGTCTGC CGCCGCCGCT CCGTCTGCA GGAATACAAC  
CGCGCGCTTA TTTGACGACG CGCGCGGCGA GGCAGGACGT CCTTATGTTG

33851 ATGGCAGTGG TCTCCTCAGC GATGATTGCG ACCGCCGCA GCATAAGGCG  
TACCGTCACC AGAGGAGTCG CTAATAAGCG TGGCGGGCGT CGTATTCCGC

33901 CCTTGTCTC CGGGCACAGC AGCGCACCCCT GATCTCACTT AAATCAGCAC  
GGAACAGGAG GCGCGTGTG TCGCGTGGGA CTAGAGTGAA TTTAGTCGTG

33951 AGTAACTGCA GCACAGCACC ACAATATTGT TCAAAATCCC ACAGTGCAAG  
TCATTGACGT CGTGTGCTGG TGTATAACA AGTTTATAGG TGTCACGTTC

34001 GCGCTGTATC CAAAGCTCAT GCGGGGGACC ACAGAACCCA CGTGCCATC  
CGCGACATAG GTTTCGAGTA CCGCCCCCTG TGTCTTGGGT GCACCGGTAG

34051 ATACCACAAG CGCAGGTAGA TTAAGTGGCG ACCCCTCATA AACACGCTGG  
TATGGTGTTC GCGTCCATCT AATTCACCGC TGGGGAGTAT TTGTGCGACC

34101 ACATAAACAT TACCTCTTTT GGCATGTTGT AATTCACCAC CTCCCGGTAC  
TGTATTTGTA ATGAGAAAA CCGTACAACA TTAAGTGGTG GAGGGCCATG

Figure 26 AJ

34151 CATATAAACC T GATTAAA CATGGCGCCA TCCACCACCA TCCTAATCA  
 GTATATTGG AACTAATTT GTACCGCGGT AGGTGGTGGT AGGATTCT  
 34201 GCTGGCCAAA ACCTGCCCCG CGGCTATACA CTGCAGGGAA CCGGGACTGG  
 CGACCGSTTT TGGACGGGCG GCCGATATGT GACGTCCCTT GGCCTGACC  
 34251 AACAATGACA GTGGAGAGCC CAGGACTCGT AACCATGGAT CATCATGCTC  
 TTGTTACTGT CACCTCTCGG GTCCTGAGCA TTGGTACCTA GTAGTACGAG  
 34301 GTCATGATAT CAATGTTGGC ACAACACAGG CACACGTGCA TACACTTCCT  
 CAGTACTATA GTTACAACCG TGTGTGTGCC GTGTGCACGT ATGTGAAGGA  
 34351 CAGGATTACA AGCTCCTCCC GCGTTAGAAC CATATCCCAG GGAACAACCC  
 GTCCTAATGT TCGAGGAGGG CGCAATCTTG GTATAGGGTC CCTTGTGGG  
 34401 ATTCTTGAAT CAGCGTAAAT CCCACACTGC AGGGAAGACC TCGCACGTAA  
 TAAGGACTTA GTCGCATTTA GGGTGTGACG TCCCTTCTGG AGCGTGCATT  
 34451 CTCACGTTGT GCATTGTCAA AGTGTTACAT TCGGGCAGCA GCGGATGATC  
 GAGTGAACA CGTAACASTT TCACAATGTA AGCCCGTCGT CGCCTACTAG  
 34501 CTCCAGTATG GTAGCGCGGG TTTCTGTCTC AAAAGGAGGT AGACGATCCC  
 GAGGTCATAC CATCGCGCCC AAAGACAGAG TTTTCTCCA TCTGCTAGGG  
 34551 TACTGTACGG AGTGCGCCGA GACAACCGAG ATCGTGTGG TCGTAGTGTG  
 ATGACATGCC TCACGCGGCT CTGTTGGCTC TAGCACAACC AGCATCACAG  
 34601 ATGCCAAATG GAACGCCCGA CGTAGTCATA TTTCTGAAG CAAAACCAGG  
 TACGGTTTAC CTGCGGGCCT GCATCAGTAT AAAGGACTTC GTTTTGGTCC  
 34651 TCGCGGCGTG ACAACAGAT CTGCGTCTCC GGTCTCGCGG CTTAGATCGC  
 ACGCCCCGAC TGTGTGTCTA GACGCAGAGG CCAGAGCGGC GAATCTAGCG  
 34701 TCTGTGTAGT AGTTGTAGTA TATCCACTCT CTCAAAGCAT CCAGGCGCCC  
 AGACACATCA TCAACATCAT ATAGGTGAGA GAGTTTCGTA GGTCCGCGGG  
 34751 CCTGGCTTCG GGTCTATGT AACTCCTTC ATGCGCGGCT GCCCTGATAA  
 GGACCGAAGC CCAAGATACA TTGAGGAAG TACGCGGCGA CGGGACTATT  
 34801 CATCCACCAC CGCAGAATAA GCCACACCCA GCCAACCTAC ACATTGCTTC  
 GTAGGTGGTG GCGTCTTATT CGGTGTGGGT CGGTTGGATG TGTAAGCAAG  
 34851 TCGGAGTCAC ACACGGGAGG AGCGGGAAGA GCTGGAAGAA CCATGTTTTT  
 ACGCTCAGTG TGTGCCCTCC TCGCCCTTCT CGACCTTCTT GGTACAAAAA  
 34901 TTTTTTATTC CAAAAGATTA TCCAAAACCT CAAAATGAAG ATCTATTAAG  
 AAAAAATAAG GTTTTCTAAT AGGTTTGGGA GTTTTACTTC TAGATAATTC  
 34951 TGAACGCGCT CCCCTCCGGT GCGGTGGTCA AACTCTACAG CCAAAGAACA  
 ACTTGCGCGA GGGGAGGCCA CCGCACCAGT TTGAGATGTC GGTTCCTTGT  
 35001 GATAATGGCA TTTGTAAGAT GTTGCACAA GTGCTTCCAA AGGCAAACGG  
 CTATTACCGT AAACATTCTA CAACGTGTTA CCGAAGGTTT TCCGTTTGCC  
 35051 CCCTCACGTC CAAGTGGACG TAAAGGCTAA ACCCTTCAGG GTGAATCTCC  
 GGGAGTGCAG GTTCACCTGC ATTTCCGATT TGGGAAGTCC CACTTAGAGG

Figure 26 AK

35101 TCTATAAACA TTTAGCACC TTCAACCATG CCCAAATAAT TCTCATTTG  
 AGATATTTGT AAGGTCGTGG AAGTTGCTAC GGGTTTATTA AGAGTAGAGC  
 35151 CCACCTTCTC AATATATCTC TAAGCAAATC CCGAATATTA AGTCCGGCCA  
 GGTGGAAGAG TTATATAGAG ATTCGTTAG GGCTTATAAT TCAGGCCGGT  
 35201 TTGTAAAAAT CTGCTCCAGA GCGCCCTCCA CCTTCAGCCT CAAGCAGCGA  
 AACATTTTTA GACGAGGTCT CGCGGGAGGT GGAAGTCGGA GTTCGTCGCT  
 35251 ATCATGATTG CAAAAATTCA GGTTCCTCAC AGACCTGTAT AAGATTCAAA  
 TAGTACTAAC GTTTTAAAGT CCAAGGAGTG TCTGGACATA TTCTAAGTTT  
 35301 AGCGGAACAT TAACAAAAAT ACCGCGATCC CGTAGGTCCC TTCGCAGGGC  
 TCGCCTTGTA ATTGTTTTTA TGGCGCTAGG GCATCCAGGG AAGCGTCCCG  
 35351 CAGCTGAACA TAATCGTGCA GGTCTGCACG GACCAGCGCG GCCACTTCCC  
 GTCGACTTGT ATTAGCACGT CCAGACGTGC CTGGTCGCGC CGGTGAAGGG  
 35401 CGCCAGGAAC CATGACAAAA GAACCCACAC TGATTATGAC ACGCATACTC  
 GCGGTCCTTG GACTGTGTTT CTTGGGTGTG ACTAATACTG TCGGTATGAG  
 35451 GGAGCTATGC TAACCAGCGT AGCCCCGATG TAAGCTTGTT GCATGGGCGG  
 CCTCGATACG ATTGGTCGCA TCGGGGCTAC ATTGGAACAA CGTACCCGCC  
 35501 CGATATAAAA TGCAAGGTGC TGCTCAAAAA ATCAGGCAAA GCCTCGCGCA  
 GCTATATTTT ACGTTCACG ACGAGTTTTT TAGTCCGTTT CGGAGCGCGT  
 35551 AAAAAGAAAG CACATCGTAG TCATGCTCAT GCAGATAAAG GCAGGTAAGC  
 TTTTCTTTT GTGTAGCATC AGTACGAGTA CGTCTATTTC CGTCCATTTC  
 35601 TCCGGAACCA CCACAGAAAA AGACACCATT TTTCTCTCAA ACATGTCTGC  
 AGGCCTTGGT GGTGTCTTTT TCTGTGGTAA AAAGAGAGTT TGTACAGACG  
 35651 GGGTTTCTGC ATAAACACAA AATAAAATAA CAAAAAACA TTTAAACATT  
 CCCAAAGACG TATTTGTGTT TTATTTTATT GTTTTTTTGT AAATTTGTAA  
 35701 AGAAGCCTGT CTTACAACAG GAAAAACAAC CCTTATAAGC ATAAGACGGA  
 TCTTCGGACA GAATGTTGTC CTTTTTGTTG GGAATATTTC TATTCGCTCT  
 35751 CTACGGCCAT GCCGGCGTGA CCGTAAAAAA ACTGGTCACC GTGATTAAAA  
 GATGCCGGTA CGGCCGCACT GGCATTTTTT TGACCAGTGG CACTAATTTT  
 35801 AGCACCACCG ACAGCTCCTC GGTCTGTGCC GGAGTCATAA TGTAAAGACTC  
 TCGTGGTGGC TGTCGAGGAG CCACTACAGG CCTCAGTATT ACATTCTGAG  
 35851 GGTAAACACA TCAGGTTGAT TCACATCGGT CAGTGCTAAA AAGCGACCGA  
 CCAATTGTGT AGTCCAACATA AGTGTAGCCA GTCACGATTT TTCGCTGGCT  
 35901 AATAGCCCGG GGAATACAT ACCCGCAGGC GTAGAGACAA CATTACAGCC  
 TTATCGGGCC CCCTTATGTA TGGGCGTCCG CATCTCTGTT GTAAATGTCGG  
 35951 CCCATAGGAG GTATAACAAA ATTAATAGGA GAGAAAAACA CATAAACACC  
 GGGTATCCTC CATATTGTTT TAATTATCCT CTCTTTTTGT GTATTTGTGG  
 36001 TGAAAAACCC TCCTGCCTAG GCAAAATAGC ACCCTCCCGC TCCAGAACAA  
 ACTTTTTGGG AGGACGGATC CGTTTTATCG TGGGAGGGCG AGGTCTTGTT

Figure 26 AL

36051 CATACAGCGC TACAGCG GCAGCCATAA CAGTCAGCCT TACCAG LA  
 GTATGTCGCG AAGGTGTCGC CGTCGGTATT GTCAGTCGGA ATGGTCATTT

36101 AAAGAAAACC TATTAACAAA ACACCACTCG ACACGGCACC AGCTCAATCA  
 TTCTTTTGG ATAATTTTTT TGTGGTGAGC TGTGCCGTGG TCGAGTTAGT

36151 GTCACAGTGT AAAAAAGGCG CAAGTGCAGA GCGAGTATAT ATAGGACTAA  
 CAGTGTACACA TTTTTCCTCG GTTCACGTCT CGCTCATATA TATCCTGATT

36201 AAAATGACGT AACGGTTAAA GTCCACAAA AACACCCAGA AAACCGCACG  
 TTTTACTGCA TTGCCAATTT CAGGTGTTTT TTGTGGGTCT TTTGGCGTGC

36251 CGAACCTACG CCCAGAAACG AAAGCCAAAA AACCCACAAC TTCCTCAAAT  
 GCTTGGATGC GGGTCTTTGC TTTGGGTTTT TTGGGTGTTG AAGGAGTTTA

36301 CGTCACTTCC GTTTTCCAC GTTACGTCAC TTCCCATTTT AAGAAACTA  
 GCAGTGAAGG CAAAAGGGTG CAATGCAGTG AAGGGTAAAA TTCTTTTGAT

36351 CAATTCCCAA CACATACAAG TTAATCCGCC CTAAACCTA CGTCACCCGC  
 GTTAAGGGTT GTGTATGTTT AATGAGGCGG GATTTTGAT GCAGTGGGCG

36401 CCCGTTCCCA CGCCCCGCGC CACGTCACAA ACTCCACCCC CTCATTATCA  
 GGGCAAGGGT GCGGGGCGCG GTGCAGTGT TGAGGTGGG GAGTAATAGT

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36451 TATTGGCTTC AATCCAAAAT AAGGTATATT ATTGATGATG TTAATTAAGA  
 ATAACCGAAG TTAGGTTTTA TTCCATATAA TAACTACTAC AATTAATTCT

36501 ATTGGGATCT GCGACGCGAG GCTGGATGGC CTTCCCCATT ATGATTCTTC  
 TAAGCCTAGA CGCTGCGCTC CGACCTACCG GAAGGGGTAA TACTAAGAAG

36551 TCGCTTCCGG CGGCATCGGG ATGCCCGCGT TGCAGGCCAT GCTGTCCAGG  
 AGCGAAGGCC GCCGTAGCCC TACGGGCGCA ACGTCCGGTA CGACAGGTCC

36601 CAGGTAGATG ACGACCATCA GGGACAGCTT CAAGGCCAGC AAAAGGCCAG  
 GTCCATCTAC TGCTGGTAGT CCCTGTCGAA GTTCCGGTCG TTTTCCGGTC

36651 GAACCGTAAA AAGGCCGCGT TGCTGGCGTT TTTCCATAGG CTCCGCCCCC  
 CTTGGCATTT TTCCGGCGCA ACGACCGCAA AAAGGTATCC GAGGCGGGGG

36701 CTGACGAGCA TCACAAAAAT CGACGCTCAA GTCAGAGGTG GCGAAACCCG  
 GACTGCTCGT AGTGTTTTTA GCTGCGAGTT CAGTCTCCAC CGCTTTGGGC

36751 ACAGGACTAT AAAGATACCA GGCCTTTCCC CCTGGAAGCT CCCTCGTGCG  
 TGTCTGATA TTTCTATGGT CCGCAAAGGG GGACCTTCGA GGGAGCACGC

36801 CTCTCTGTT CCGACCTGCG CGCTTACCGG ATACCTGTCC GCCTTTCTCC  
 GAGAGGACAA GGTGGGACG GCGAATGGCC TATGGACAGG CGGAAGAGG

36851 CTTGGGGAAG CGTGGCGCTT TCTCATAGCT CACGCTGTAG GTATCTCAGT  
 GAAGCCCTTC GCACCGCGAA AGAGTATCGA GTGCGACATC CATAGAGTCA

36901 TCGGTGTAGG TCGTTCGCTC CAAGCTGGGC TGTGTGCACG AACCCCGCGT  
 AGCCACATCC AGCAAGCGAG GTTCGACCCG ACACACGTGC TTGGGGGGCA

Figure 26 AM

36951 TCAGCCCGAC GTCGCGCT TATCCGGTAA CTATCGTCTT GAGTCGCGC  
AGTCGGGCTG GCGACGCGGA ATAGGCCATT GATAGCAGAA CTCAGGCTGG

37001 CGGTAAGACA CGACTTATCG CCACTGGCAG CAGCCACTGG TAACAGGATT  
GCCATTCTGT GCTGAATAGC GGTGACCGTC GTCGGTGACC ATTGTCCTAA

37051 AGCAGAGCGA GGTATGTAGG CGGTGCTACA GAGTTCTTGA AGTGGTGGCC  
TCGTCTCGCT CCATACATCC GCCACGATGT CTCAAGAAGT TCACCACCGG

37101 TAACTACGGC TACACTAGAA GGACAGTATT TGGTATCTGC GCTCTGCTGA  
ATTGATGCCG ATGTGATCTT CCTGTCATAA ACCATAGACG CGAGACGACT

37151 AGCCAGTTAC CTTCGGAAAA AGAGTTGGTA GCTCTTGATC CGGCAAAACA  
TCGGTCAATG GAAGCCTTTT TCTCAACCAT CGAGAAGTAG GCCGTTTGTT

37201 ACCACCCTG GTAGCGGTGG TTTTTTTGTT TGCAAGCAGC AGATTACGGC  
TGGTGGCGAC CATCGCCACC AAAAAACAA ACGTTCGTCG TCTAATGCGC

37251 CAGAAAAAAA GGATCTCAAG AAGATCCTTT GATCTTTTCT ACGGGGTCTG  
GTCTTTTTTT CCTAGAGTTC TTCTAGGAAA CTAGAAAAGA TGCCCCAGAC

37301 ACGCTCAGTG GAACGAAAAC TCACGTTAAG GGATTTTGGT CATGAGATTA  
TGCGAGTCAC CTTGCTTTTG AGTGCAATTC CCTAAAACCA GTACTCTAAT

37351 TCAAAAAGGA TCTTCACCTA GATCCTTTTA AATCAATCTA AAGTATATAT  
AGTTTTCTCT AGAAGTGGAT CTAGGAAAAT TTAGTTAGAT TTCATATATA

37401 GAGTAACTT GGTCTGACAG TTACCAATGC TTAATCAGTG AGGCACCTAT  
CTCATTGAA CCAGACTGTC AATGGTTACG AATTAGTCAC TCCGTGATA

37451 CTCAGCGATC TGTCTATTTC GTTCATCCAT AGTTGCCTGA CTCCCCGTG  
GAGTCGCTAG ACAGATAAAG CAAGTAGGTA TCAACGGACT GAGGGGCAGC

37501 TGTAAGATAAC TACGATACGG GAGGGCTTAC CATCTGGCCC CAGTGCTGCA  
ACATCTATTG ATGCTATGCC CTCCGAATG GTAGACCGGG GTCACGACGT

37551 ATGATACCGC GAGACCCACG CTCACCGGCT CCAGATTTAT CAGCAATAAA  
TACTATGGCG CTCTGGGTGC GAGTGGCCGA GGTCTAAATA GTCGTTATTT

37601 CCAGCCAGCC GGAAGGGCCG AGCGCAGAAG TGGTCTGCA ACTTTATCCG  
GGTCGGTCGG CCTTCCCGGC TCGCGTCTTC ACCAGGACGT TGAAATAGGC

37651 CCTCCATCCA GTCTATTAAAT TGTTGCCGGG AAGCTAGAGT AAGTAGTTCG  
GGAGGTAGGT CAGATAATTA ACAACGGCCC TTCGATCTCA TTCATCAAGC

37701 CCAGTTAATA GTTTGCGCAA CGTTGTTGCC ATTGCTACAG GCATCGTGGT  
GGTCAATTAT CAAACGCGTT GCAACAACGG TAACGATGTC CGTAGCACCA

37751 GTCACGCTCG TCGTTTGTA TGGCTTCATT CAGCTCCGGT TCCCAACGAT  
CAGTGCAGAC AGCAAACCAT ACCGAAGTAA GTCGAGGCCA AGGGTTGCTA

37801 CAAGGCGAGT TACATGATCC CCCATGTTGT GCAAAAAAGC GGTAGCTCC  
GTTCCGCTCA ATGTACTAGG GGGTACAACA CGTTTTTTTCG CCAATCGAGG

37851 TTCGGTCCTC CGATCGTTGT CAGAAGTAA GTGGCCGAG TGTATCACT  
AAGCCAGGAG GCTAGCAACA GTCTTCATTC AACCAGCGTC ACAATAGTGA

Figure 26 AN

37901 CATGGTTATG CCACTGC ATAATTCTCT TACTGTGATG CCAATCCAA  
GTACCAATAC CGTCGTGACG TATTAAGAGA ATGACAGTAC GGTAGGCATT

37951 GATGCTTTTC TGTGACTGGT GAGTACTCAA CCAAGTCATT CTGAGAATAG  
CTACGAAAAG ACACTGACCA CTCATGAGTT GGTTCAGTAA GACTCTTATC

38001 TGTATGCGGC GACCGAGTTG CTCTTGCCCG GCGTCAACAC GGGATAATAC  
ACATACGCCG CTGGCTCAAC GAGAACGGGC CGCAGTTGTG CCCTATTATG

38051 CGCGCCACAT AGCAGAACTT TAAAAGTGCT CATCATTGGA AAACGTTCTT  
GCGCGGTGTA TCGTCTTGAA ATTTTCACGA GTAGTAACCT TTTGCAAGAA

38101 CGGGGCGAAA ACTCTCAAGG ATCTTACCGC TGTGAGATC CAGTTCGATG  
GCCCCGCTTT TGAGAGTTCC TAGAATGGCG ACAACTCTAG GTCAAGCTAC

38151 TAACCCACTC GTGCACCCAA CTGATCTTCA GCATCTTTTA CTTTCACCAG  
ATTGGGTGAG CACGTGGGTT GACTAGAAGT CGTAGAAAAT GAAAGTGGTC

38201 CGTTTCTGGG TGAGCAAAAA CAGGAAGGCA AAATGCCGCA AAAAAGGGAA  
GCAAAGACCC ACTCGTTTTT GTCCTTCCGT TTTACGGCGT TTTTTCCTT

38251 TAAGGGCGAC ACGGAAATGT TGAATACTCA TACTCTTCCT TTTTCAATAT  
ATTCCCGCTG TGCCTTTACA ACTTATGAGT ATGAGAAGGA AAAAGTTATA

38301 TATTGAAGCA TTTATCAGGG TTATTGTCTC ATGAGCGGAT ACATATTTGA  
ATAACTTCGT AAATAGTCCC AATAACAGAG TACTCGCCTA TGTATAAACT

38351 ATGTATTTAG AAAAATAAAC AAATAGGGGT TCCGCGCACA TTTCCCCGAA  
TACATAAATC TTTTATTGTT TTTATCCCCA AGGCGCGTGT AAAGGGGCTT

38401 AAGTGCCACC TGACGTCTAA GAAACCATTA TTATCATGAC ATTAACTAT  
TTCACGGTGG ACTGCAGATT CTTTGGTAAT AATAGTACTG TAATTGGATA

38451 AAAAATAGGC GTATCACGAG GCCCTTTCGT CTTCAAGAAT TGGATCCGAA  
TTTTTATCCG CATAGTGCTC CGGGAAAGCA GAAGTTCTTA ACCTAGGCTT

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38501 TTCTTAATTT CTTAATTAA (SEQ ID NO:32)  
AAGAATTAAA GAATTAATT (SEQ ID NO:33)

Figure 26 A0

MRKAd5nef MER1063  
(MRKAd5 Pre-Adenoviral Vector Containing the G2A,LLA nef Coding Region)

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1  CATCATCAAT AATATACCTT ATTTTGGATT GAAGCCAATA TGATAATGAG
   GTAGTAGTTA TTATATGGAA TAAAACCTAA CTTCGGTTAT ACTATTACTC

51  GGGGTGGAGT TTGTGACGTG GCGCGGGGCG TGGGAACGGG GCGGGTGACG
   CCCACCTCA AACACTGCAC CGCGCCCGC ACCCTTGCCC CGCCCACTGC

101 TAGTAGTGTG GCGGAAGTGT GATGTTGCAA GTGTGGCGGA ACACATGTAA
   ATCATCACAC CGCCTTCACA CTACAACGTT CACACCGCCT TGTGTACATT

151 GCGACGGATG TGGCAAAAGT GACGTTTTTG GTGTGCGCCG GTGTACACAG
   CGCTGCCTAC ACCGTTTTCA CTGCAAAAAC CACACGCGGC CACATGTGTC

201 GAAGTGACAA TTTTCGCGCG GTTTTAGGCG GATGTTGTAG TAAATTTGGG
   CTTCACTGTT AAAAGCGCGC CAAAATCCGC CTACAACATC ATTTAAACCC

251 CGTAACCGAG TAAGATTGCG CCATTTTCGC GGGAAAAC TG AATAAGAGGA
   GCATTGGCTC ATTCTAAACC GGTAAAAGCG CCCTTTTGAC TTATTCTCCT

301 AGTGAATCT GAACAATTTT GTGTTACTCA TAGCGCGTAA TATTGTCTA
   TCACTTTAGA CTTATTAAAA CACAATGAGT ATCGCGCATT ATAAACAGAT

351 GGGCCGCGGG GACTTTGACC GTTTACGTGG AGACTCGCCC AGGTGTTTTT
   CCCGCGCCCC CTGAACTGG CAAATGCACC TCTGAGCGGG TCCACAAAAA

401 CTCAGTGTTT TTCCGCGTTC CGGGTCAAAG TTGGCGTTTT ATTATTATAG
   GAGTCCACAA AAGGCGCAAG GCCCAGTTTC AACCGCAAAA TAATAATATC

451 GCGGCGCGCA TCCATTGCAT ACGTTGTATC CATATCATAA TATGTACATT
   CGCCGCGCCT AGGTAACGTA TGCAACATAG GTATAGTATT ATACATGTAA

501 TATATTGGCT CATGTCCAAC ATTACCGCCA TGTGACATT GATTATTGAC
   ATATAACCGA GTACAGGTTG TAATGGCGGT ACAACTGTAA CTAATAACTG

551 TAGTTATTAA TAGTAATCAA TTACGGGGTC ATTAGTTCAT AGCCCATATA
   ATCAATAATT ATCATTAGTT AATGCCCCAG TAATCAAGTA TCGGGTATAT

601 TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG
   ACCTCAAGGC GCAATGTATT GAATGCCATT TACCGGGCGG ACCGACTGGC

651 CCCAACGACC CCCGCCCAT GACGTCAATA ATGACGTATG TTCCCATAGT
   GGGTTGCTGG GGGCGGGTAA CTGCAGTTAT TACTGCATAC AAGGGTATCA

701 AACGCCAATA GGGACTTTCC ATTGACGTCA ATGGGTGGAG TATTTACGGT
   TTGCGGTTAT CCCTGAAAGG TAACTGCAGT TACCCACCTC ATAAATGCCA

751 AAAGTCCCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC AAGTACGCCC
   TTTGACGGGT GAACCGTCAT GTAGTTCACA TAGTATACGG TTCATGCGGG

801 CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCCAGTA
   GGATAACTGC AGTTACTGCC ATTTACGGG CGGACCGTAA TACGGGTCAT

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*Figure 27A*

851 CATGACCTTA TACTTTC CTA~~CT~~TGSCA GTACATCTAC GTATT~~TA~~TA  
 GTACTGGAAT A~~CT~~CTGAAAG GATGAACCGT CATGTAGATG CATAATCAGT

901 TCGCTATTAC CATGGTGATG CGGTTTTGGC AGTACATCAA TGGGCGTGGA  
 AGCGATAATG GTACCACTAC GCCAAAACCG TCATGTAGTT ACCCGCACCT

951 TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA  
 ATCGCCAAAC TGAGTGCCCC TAAAGGTTCA GAGGTGGGGT AACTGCAGTT

1001 TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA  
 ACCCTCAAAC AAAACCGTGG TTTTAGTTGC CCTGAAAGGT TTTACAGCAT

1051 ACAACTCCGC CCCATTGACG CAAATGGGCG GTAGGCGTGT ACGGTGGGAG  
 TGTGAGGGCG GGGTAACTGC GTTTACCCGC CATCCGCACA TGCCACCCTC

1101 GTCTATATAA GCAGAGCTCG TTTAGTGAAC CGTCAGATCG CCTGGAGACG  
 CAGATATATT CGTCTCGAGC AAATCACTTG GCAGTCTAGC GGACCTCTGC

1151 CCATCCACGC TGTTTTGACC TCCATAGAAG ACACCGGGAC CGATCCAGCC  
 GGTAGGTGCG ACAAACTGG AGGTATCTTC TGTGGCCCTG GCTAGGTGCG

1201 TCCGCGGCGG GGAACGGTGC ATTGGAACGC GGATTCCCGG TGCCAAGAGT  
 AGGCGCCGGC CCTTGCCACG TAACCTTGCG CCTAAGGGGC ACGGTTCTCA

1251 GAGATCTGCC ACCATGGCCG GCAAGTGGTC CAAGAGGTCC GTGCCCGGCT  
 CTCTAGACGG TGGTACCGGC CGTTCACCAG GTTCTCCAGG CACGGGCCGA

1301 GGTCCACCGT GAGGGAGAGG ATGAGGAGGG CCGAGCCCGC CGCCGACAGG  
 CCAGGTGGCA CTCCTCTCC TACTCCTCCC GGCTCGGGCG GCGGCTGTCC

1351 GTGAGGAGGA CCGAGCCCGC CGCAGTGGGC GTGGGCGCGG TGTCCAGGGA  
 CACTCCTCCT GGCTCGGGCG GCGTCACCGC CACCCGCGGC ACAGGTCCCT

1401 CCTGGAGAAG CACGGCGCCA TCACCTCCTC CAACACCGCC GCCACCAACG  
 GGACCTCTTC GTGCCGCGGT AGTGGAGGAG GTTGTGGCGG CGGTGGTTGC

1451 CCGACTGCGC CTGGCTGGAG GCCCAGGAGG ACGAGGAGGT GGGCTTCCCC  
 GGCTGACGCG GACCGACCTC CGGGTCTCC TGCTCCTCCA CCCGAAGGGG

1501 GTGAGGCCCC AGGTGCCCTT GAGGCCCATG ACCTACAAGG GCGCCGTGGA  
 CACTCCGGGG TCCACGGGGA CTCCGGGTAC TGGATGTTCC CGCGGCACCT

1551 CCTGTCCAC TTCTGAAGG AGAAGGGCGG CCTGGAGGGC CTGATCCACT  
 GGACAGGGTG AAGGACTTCC TCTTCCCGC GGACCTCCCG GACTAGGTGA

1601 CCCAGAAGAG GCAGGACATC CTGGACCTGT GGGTGTACCA CACCCAGGGC  
 GGGTCTTCTC CGTCTGTAG GACCTGGACA CCCACATGGT GTGGGTCCCG

1651 TACTTCCCCG ACTGGCAGAA CTACACCCCC GGCCCCGGCA TCAGGTTCCC  
 ATGAAGGGGC TGACCGTCTT GATGTGGGGG CCGGGGCCGT AGTCCAAGGG

1701 CCTGACCTTC GGCTGGTGCT TCAAGCTGGT GCCCGTGGAG CCCGAGAAGG  
 GGACTGGAAG CCGACCACGA AGTTCGACCA CGGGCACCTC GGGCTCTTCC

1751 TGGAGGAGGC CAACGAGGGC GAGAACAAC TCGCCGCCCA CCCCATGTCC  
 ACCTCCTCCG GTTGCTCCCG CTCTTGTTGA CGCGCGGGT GGGGTACAGG

Figure 27B

1801 CAGCACGGCA TGGACCC CGAGAAGGAG GTGCTGGAGT GGAGGTGSA  
 GTCGTGCCGT AGCTCCTGGG GCTCTTCCTC CACGACCTCA CCTCCAAAGCT  
 1851 CTCCAAGCTG GCCTTCCACC ACGTGGCCAG GGAGCTGCAC CCCGAGTACT  
 GAGGTTTCGAC CGGAAGGTGG TGCACCGGTC CCTCGACGTG GGGCTCATGA  
 1901 ACAAGGACTG CTAAAGCCCG GGCAGATCTG CTGTGCCTTC TAGTTGCCAG  
 TGTTCCTGAC GATTTCCGGC CCGTCTAGAC GACACGGAAG ATCAACGGTC  
 1951 CCATCTGTTG TTGCCCCCTC CCCCCTGCCT TCCTTGACCC TGGAAAGGTGC  
 GGTAGACAAC AAACGGGGAG GGGGCACGGA AGGAACTGGG ACCTTCCACG  
 2001 CACTCCCCTG GTCTTTTCTT AATAAAATGA GGAAATTGCA TCGCATTGTC  
 GTGAGGCTGA CAGGAAGGA TTATTTTACT CCTTTAACGT AGCGTAACAG  
 2051 TGAGTAGGTG TCATTCTATT CTGGGGGGTG GGGTGGGGCA GGACAGCAAG  
 ACTCATCCAC AGTAAGATAA GACCCCCCAC CCCACCCCGT CCTGTCGTTC  
 2101 GGGGAGGATT GGAAGACAA TAGCAGGCAT GCTGGGGATG CGGTGGGCTC  
 CCCCTCTTAA CCCTTCTGTT ATCGTCCGTA CGACCCCTAC GCCACCCGAG  
 2151 TATGGCCGAT CGGCGCGCCG TACTGAAATG TGTGGGCGTG GCTTAAGGGT  
 ATACCGGCTA GCCGCGCGGC ATGACTTTAC ACACCCGCAC CGAATTCCCA  
 2201 GGGAAAGAAT ATATAAGGTG GGGGTCTTAT GTAGTTTTGT ATCTGTTTTG  
 CCCTTTCTTA TATATTCCAC CCCAGAATA CATCAAAACA TAGACAAAAC  
 2251 CAGCAGCCGC CGCCGCCATG AGCACCACCT CGTTTGATGG AAGCATTGTG  
 GTCGTCCGCG GCGGCGGTAC TCGTGGTTGA GCAAACCTACC TTCGTAACAC  
 2301 AGCTCATATT TGACAACCGC CATGCCCCCA TGGGCCGGGG TGCCTCAGAA  
 TCGAGTATAA ACTGTTGCGC GTACGGGGGT ACCCGGCCCC ACGCAGTCTT  
 2351 TGTGATGGG TCCAGCATTG ATGGTCGCCC CGTCCTGCCC GCAAACCTCTA  
 ACACIACCCG AGGTGCTAAC TACCAGCGGG GCAGGACGGG CGTTTGAGAT  
 2401 CTACCTTGAC CTACGAGACC GTGTCTGGAA CGCCGTTGGA GACTGCAGCC  
 GATGGAACCTG GATGCTCTGG CACAGACCTT GCGGCAACCT CTGACGTCGG  
 2451 TCCGCCGCGC CTTCAGCCGC TGCAGCCACC GCCCGCGGGA TTGTGACTGA  
 AGGCGGCGGC GAAGTCGGCG ACGTCGGTGG CGGGCGCCCT AACACTGACT  
 2501 CTTTGCTTTC CTGAGCCCGC TTGCAACAG TGCAGCTTCC CGTTCATCCG  
 GAAACGAAAG GACTCGGGCG AACGTTTGTG ACCTCGAAGG GCAAGTAGGC  
 2551 CCCGCGATGA CAAGTTGACG GCTCTTTTGG CACAATTGGA TTCTTTGACC  
 GGGCGCTACT GTTCAACTGC CGAGAAAACC GTGTTAACCT AAGAAACTGG  
 2601 CGGGAACCTA ATGTCGTTTC TCAGCAGCTG TTGGATCTGC GCCAGCAGST  
 GCCCTTGAAT TACAGCAAAG AGTCGTCGAC AACCTAGACG CGGTGCTCCA  
 2651 TTCTGCCCTG AAGGCTTCCT CCCCTCCCAA TCGGTTTTAA AACATAAATA  
 AAGACGGGAC TTCCGAAGGA GGGGAGGGT ACGCCAAATT TTGTATTTAT  
 2701 AAAAACGAGA CTCTGTTTGG ATTTGGATCA AGCAAGTGTC TTGCTGTCTT  
 TTTTGTGCTCT GAGACAAACC TAAACCTAGT TCCTTCACAG AACGACAGAA

Figure 27C

2751 TATTTAGGGG TTTTGGCGCG GCGGTAGGCC CGGGACCAGC GGTCTCGGTC  
 ATAAATCCCC AAAACGCGCG CGCCATCCGG GCCCTGGTCG CCAGAGCCAG  
 2801 GTTGAAGGTC CTGTGTATTT TTTCCAGGAC GTGGTAAAGG TGACTCTGGA  
 CAACTCCCAG GACACATAAA AAAGGTCCTG CACCATTTC CACTGAGACCT  
 2851 TGTTCAGATA CATGGGCATA AGCCCGTCTC TGGGGTGGAG GTAGCACCAC  
 ACAAGTCTAT GTACCCGTAT TCGGGCAGAG ACCCCACCTC CATCGTGGTG  
 2901 TGCAGAGCTT CATGCTGCGG GGTGGTGTGTG TAGATGATCC AGTCGTAGCA  
 ACGTCTCGAA GTACGACGCC CCACCACAAC ATCTACTAGG TCAGCATCGT  
 2951 GGAGCGCTGG GCGTGGTGCC TAAAAATGTC TTTCACTAGC AAGCTGATTG  
 CCTCGCGACC CGCACCACGG ATTTTACAG AAAGTCATCG TTCGACTAAC  
 3001 CCAGGGGCAG GCCCTTGGTG TAAGTGTTTA CAAAGCGGTT AAGCTGGGAT  
 GGTCCCCGTC CGGGAACCAC ATTCACAAAT GTTTCGCCAA TTCGACCCTA  
 3051 GGGTGCATAC GTGGGGATAT GAGATGCATC TTGGACTGTA TTTTtaggTT  
 CCCACGTATG CACCCCTATA CTCTACGTAG AACCTGACAT AAAAATCCAA  
 3101 GGCTATGTTT CCAGCCATAT CCCTCCGGGG ATTCACTGTG TGCAGAACCA  
 CCGATACAAG GGTCCGTATA GGGAGGCCCC TAAGTACAAC ACGTCTTGGT  
 3151 CCAGCACAGT GTATCCGGTG CACTTGGGAA ATTGTGTCATG TAGCTTAGAA  
 GGTCTGTGCA CATAGGCCAC GTGAACCCCT TAAACAGTAC ATCGAATCTT  
 3201 GGAAATGCGT GGAAGAACTT GGAGACGCCC TTGTGACCTC CAAGATTTTC  
 CCTTTACGCA CCTTCTTGAA CCTCTCGGG AACACTGGAG GTTCTAAAAG  
 3251 CATGCATTCTG TCCATAATGA TGGCAATGGG CCCACGGGCG CGCGCCTGGG  
 GTACGTAAAG AGGTATTACT ACCGTTACCC GGGTGCCCGC CGCCGGACCC  
 3301 CGAAGATATT TCTGGGATCA CTAACGTCAT AGTTGTGTTC CAGGATGAGA  
 GCTTCTATAA AGACCCTAGT GATTGCAGTA TCAACACAAG GTCTTACTCT  
 3351 TCGTCATAGG CCATTTTAC AAAGCGCGGG CGGAGGGTGC CAGACTGCGG  
 AGCAGTATCC GGTAAAAATG TTTCCGCGCC CCCTCCACG GTCTGACGCC  
 3401 TATAATGGTT CCATCCGGCC CAGGGGCGTA GTTACCCCTA CAGATTTGCA  
 ATATTACCAA GGTAGGCCGG GTCCCCGAT CAATGGGAGT GTCTAAACGT  
 3451 TTTCCACGCG TTTGAGTTCA GATGGGGGGA TCATGTCTAC CTGCGGGGCG  
 AAAGGGTGGG AAACCTCAAGT CTACCCCCCT AGTACAGATG GACGCCCCGC  
 3501 ATGAAGAAAA CGGTTTCCGG GGTAGGGGAG ATCAGCTGGG AAGAAAGCAG  
 TACTTCTTTT GCCAAAGGCC CCATCCCTC TAGTCGACCC TTCTTTCTGTC  
 3551 GTTCTGAGC AGCTGCGACT TACCGCAGCC GGTGGGCCCC TAAATCACAC  
 CAAGGACTCG TCGACGCTGA ATGGCGTCGG CCACCCGGGC ATTTAGTGTG  
 3601 CTATTACCGG CTGCAACTGG TAGTTAAGAG AGCTGCAGCT GCCGTCTATC  
 GATAATGGCC GACGTTGACC ATCAATTCTC TCGACGTCGA CGGCAGTAGG  
 3651 CTGAGCAGGG GGGCCACTTC GTTAAGCATG TCCCTGACTC GCATGTTTTT  
 GACTCGTCCC CCCGGTGAAG CAATTCTGAC AGGCACTGAG CGTACAAAAG

Figure 27D

3701 CCTGACCAAA TCCAGAA GGCCTCGCC GCCCAGCGAT AGCAGTCTT  
 GGACTGGTTT AGGCGGTCTT CCGCGAGCGG CGGGTCGCTA TCGTCAAGAA  
 3751 GCAAGGAAGC AAAGTTTTTC AACGGTTTGA GACCGTCCGC CGTAGGCATG  
 CGTTCCCTTCG TTCAAAAAG TTGCCAAACT CTGGCAGGCG GCATCCGTAC  
 3801 CTTTTGAGCG TTGACCAAG CAGTTCCAGG CGGTCCCACA GCTCGGTCAC  
 GAAAACTCGC AAACCTGGTTC GTCAAGGTCC GCCAGGGTGT CGAGCCAGTG  
 3851 CTGCTCTACG GCATCTCGAT CCAGCATATC TCCTCGTTTC GCGGGTTGGG  
 GACGAGATGC CGTAGAGCTA GGTCGTATAG AGGAGCAAAG CGCCCAACCC  
 3901 GCGGCTTTTCG CTGTACGSCA GTAGTCGGTG CTCGTCCAGA CGGGCCAGGG  
 CGCCGAAAGC GACATGCCGT CATCAGCCAC GAGCAGGTCT GCCCGGTCCC  
 3951 TCATGTCTTT CCACGGGCGC AGGGTCTTCG TCAGCGTAGT CTGGGTCACG  
 AGTACAGAAA GGTGCCCGCG TCCAGGAGC AGTCGCATCA GACCCAGTGC  
 4001 GTGAAGGGGT GCGCTCCGGG CTGCGCGCTG GCCAGGGTGC GCTTGAGGCT  
 CACTTCCCCA CGCGAGGCCC GACGCGCGAC CGGTCCCACG CGAACTCCGA  
 4051 GGTCTCTGCTG GTGCTGAAGC GCTGCCGGTC TTCGCCCTGC GCGTCGGCCA  
 CCAGGACGAC CACGACTTCG CGACGGCCAG AAGCGGGACG CGCAGCCGGT  
 4101 GGTAGCATTT GACCATGGTG TCATAGTCCA GCCCCTCCGC GCGTGGCCC  
 CCATCGTAAA CTGGTACCAC AGTATCAGGT CGGGGAGGCG CCGCACCGGG  
 4151 TTGGCGCGCA GCTTGCCCTT GGAGGAGGCG CCGCACGAGG GGCAGTGCAG  
 AACC GCGCT CGAACGGGAA CCTCTCCGC GCGGTGCTCC CCGTCACGTC  
 4201 ACTTTTGAGG GCGTAGAGCT TGGGCGCGAG AAATACCGAT TCCGGGGAGT  
 TGAAAACCTCC CGCATCTCGA ACCCGCGCTC TTTATGGCTA AGGCCCTCA  
 4251 AGGCATCCGC GCCCGAGGCC CCGCAGACGG TCTCGCATTC CACGAGCCAG  
 TCCGTAGGCG CGGCGTCCGG GCGCTCTGCC AGAGCGTAAG GTGCTCGGTC  
 4301 GTGAGCTCTG GCCGTTCGGG GTCAAAAACC AGGTTTCCCC CATGCTTTTT  
 CACTCGAGAC CGGCAAGCCC CAGTTTTTGG TCCAAAGGGG GTACGAAAAA  
 4351 GATCGGTTTC TTACCTCTGG TTTCCATGAG CCGGTGTCCA CGCTCGGTGA  
 CTACGCAAAG AATGGAGACC AAAGGTACTC GGCCACAGGT GCGAGCCACT  
 4401 CGAAAAGGCT GTCCGTGTCC CCGTATACAG ACTTGAGAGG CCTGTCTCTG  
 GCTTTTCCGA CAGGCACAGG GGCATATGTC TGAACCTCTC GGACAGGAGC  
 4451 AGCGGTGTTT CCGGTCTCTC CTCGTATAGA AACTCGGACC ACTCTGAGAC  
 TCGCCACAAG GCGCCAGGAG GAGCATATCT TTGAGCCTGG TGAGACTCTG  
 4501 AAAGGCTCGC GTCCAGGCCA GCACGAAGGA GGCTAAGTGG GAGGGGTAGC  
 TTTCGAGCG CAGGTCCGGT CGTGCTTCCT CCGATTACAC CTCCCCATCG  
 4551 GGTCTGTGTC CACTAGGGGG TCCACTCGCT CCAGGGTGTG AAGACACATG  
 CCAGCAACAG GTGATCCCC AGGTGAGCGA GGTCCCACAC TTCTGTGTAC  
 4601 TCGCCCTCTT CGGCATCAAG GAAGGTGATT GGTGTGTAGG TGTAGGCCAC  
 AGCGGGAGAA GCGGTAGTTC CTCCACTAA CCAAACATCC ACATCCGGTG

Figure 27E

4651 GTGACCGGGT CCTGAAG GGGGGCTATA AAAGGGGGTG GGGGCCCTT  
 CACTGGCCCA CAAGGACTTC CCCCCGATAT TTTCCCCCAC CCCC GCGCAA  
 4701 CGTCTCACT CTCTTCCGCA TCGCTGTCTG CGAGGGCCAG CTGTTGGGGT  
 GCAGGAGTGA GAGAAGGCGT AGCGACAGAC GCTCCCGGTC GACAACCCCA  
 4751 GAGTACTCCC TCTGAAAAGC GGGCATGACT TCTGCGCTAA GATTGTCAGT  
 CTCATGAGGG AGACTTTTCG CCCGTACTGA AGACGCGATT CTAACAGTCA  
 4801 TTCCAAAAAC GAGGAGGATT TGATATTAC CTGGCCCCG GTGATGCCTT  
 AAGGTTTTTG CTCTCCTAA ACTATAAGTG GACCGGGCG CACTACGGAA  
 4851 TCAGGGTGGC CGCATCCATC TGGTCAGAAA AGACAATCTT TTTGTTGTCA  
 ACTCCCACCG GCGTAGGTAG ACCAGTCTT TCTGTTAGAA AAACAACAGT  
 4901 AGCTTGGTGG CAAACGACCC GTAGAGGGCG TTGGACAGCA ACTTGGCGAT  
 TCGAACCACC GTTTGCTGGG CATCTCCCGC AACCTGTCGT TGAACCGCTA  
 4951 GGAGCGCAGG GTTTGGTTTT TGTCGCGATC GCGCGCTCC TTGGCCGCGA  
 CCTCGCTCC CAAACCAAAA ACAGCGCTAG CCGCGCGAGG AACCGCGCT  
 5001 TGTTTAGCTG CACGTATTCTG CGCGCAACGC ACCGCCATTC GGGAAAGACG  
 ACAATCGAC GTGCATAAGC GCGCGTTGCG TGGCGGTAAG CCCTTTCTGC  
 5051 GTGGTGCCT CGTCGGGCAC CAGGTGCACG CGCCAACCGC GGTGTGTCAG  
 CACCACGCGA GCAGCCCGTG GTCCACGTGC GCGGTTGGCG CCAACACGTC  
 5101 GGTGACAAGG TCAACGCTGG TGGCTACCTC TCCGCGTAGG CGCTCGTTGG  
 CCACTGTTCC AGTTGCGACC ACCGATGGAG AGGCGCATCC GCGAGCAACC  
 5151 TCCAGCAGAG GCGGCCGCCC TTGCGCGAGC AGAATGGCGG TAGGGGGTCT  
 AGGTCTCTCT CCGCGGCGGG AACGCGCTCG TCTTACCGCC ATCCCCAGA  
 5201 AGCTGCGTCT CGTCCGGGGG GTCTGCGTCC ACGGTAAAGA CCCC GGGCAG  
 TCGACGAGA GCAGGCCCCC CAGACGCAGG TGCCATTTCT GGGGCCGTC  
 5251 CAGGCGCGCG TCGAAGTAGT CTATCTTGCA TCCTTGCAAG TCTAGCGCCT  
 GTCCGCGCGC AGCTTCATCA GATAGAAGT AGGAACGTT AGATCGCGGA  
 5301 GCTGCCATGC GCGGGCGGCA AGCGCGCGCT CGTATGGGT GAGTGGGGGA  
 CGACGGTACG CCCCCGCGT TCGCGCGCGA GCATACCCAA CTCACCCCT  
 5351 CCCCATGGCA TGGGGTGGGT GAGCGCGGAG GCGTACATGC CGCAAATGTC  
 GGGGTACCGT ACCCCACCCA CTCGCGCCTC CGCATGTACG GCGTTTACAG  
 5401 GTAAACGTAG AGGGGCTCTC TGAGTATTCC AAGATATGTA GGGTAGCATC  
 CATTTGCATC TCCCCGAGAG ACTCATAAGG TTCTATACAT CCCATCGTAG  
 5451 TTCCACCGCG GATGCTGGCG CGCACGTAAT CGTATAGTTC GTGCGAGGGA  
 AAGGTGGCGC CTACGACCGC GCGTGCAATTA GCATATCAAG CACGCTCCCT  
 5501 GCGAGGAGGT CCGGACCGAG GTTGCTACGG GCGGGCTGCT CTGCTCGGAA  
 CGCTCCTCCA GCCCTGGCTC CAACGATGCC CCGCCGACGA GACGAGCCTT  
 5551 GACTATCTGC CTGAAGATGG CATGTGAGTT GGATGATATG GTTGGACGCT  
 CTGATAGACG GACTTCTACC GTACACTCAA CCTACTATAC CAACCTGCGA

Figure 27F

5601 GGAAGACGTT CTTCTGGCG TCTGTGAGAC CTACCGCGTC ACGCACTAG  
 CCTTCTGCAA CTTTCGACCGC AGACACTCTG GATGGCGCAG TGCCTGCTTC  
 5651 GAGGCGTAGG AGTCGCCAG CTTGTTGACC AGCTCGGCGG TGACCTGCAC  
 CTCGCCATCC TCAGCGCGTC GAACAACTGG TCGAGCCGCC ACTGGACGTG  
 5701 GTCTAGGGCG CAGTAGTCCA GGGTTTCCTT GATGATGTCA TACTTATCCT  
 CAGATCCCGC GTCATCAGGT CCCAAAGGAA CTACTACAGT ATGAATAGGA  
 5751 GTCCCTTTTT TTTCCACAGC TCGCGGTTGA GGACAACTC TTCGCGGTCT  
 CAGGGAAAAA AAAGGTGTCTG AGCGCCAACT CCTGTTTGAG AAGCGCCAGA  
 5801 TTCCAGTACT CTTGGATCGG AAACCCGTCG GCCTCCGAAC GGTAAAGAGCC  
 AAGGTCATGA GAACCTAGCC TTTGGGCAGC CGGAGGCTTG CCATTCTCGG  
 5851 TAGCATGTAG AACTGGTTGA CGGCCTGTA GGCGCAGCAT CCCTTTTCTA  
 ATCGTACATC TTGACCAACT GCGCGACCAT CCGCGTCGTA GGGAAAAGAT  
 5901 CGGGTAGCGC GTATGCCTGC GCGGCCTTCC GGAGCGAGGT GTGGGTGAGC  
 GCCCATCGCG CATACGGACG CGCCGGAAGG CCTCGCTCCA CACCCACTCG  
 5951 GCAAAGGTGT CCCTGACCAT GACTTTGAGG TACTGGTATT TGAAGTCAGT  
 CTTTCCACA GGGACTGTA CTGAACTCC ATGACCATAA ACTTCAGTCA  
 6001 GTCGTCGCAT CCGCCCTGCT CCCAGAGCAA AAAGTCCGTG CGCTTTTGG  
 CAGCAGCGTA GCGGGGACGA GGGTCTCGTT TTTCAGGCAC GCGAAAAACC  
 6051 AACCGCGATT TGGCAGGGCG AAGGTGACAT CGTTGAAGAG TATCTTTCCC  
 TTGCGCTAA ACCGTCCCGC TTCCACTGTA GCAACTTCTC ATAGAAAGGG  
 6101 GCGCGAGGCA TAAAGTTGCG TGTGATGCGG AAGGGTCCCG GCACCTCGGA  
 CGCGCTCCGT ATTTCAACGC ACACTACGCC TTCCCAGGGC CGTGGAGCCT  
 6151 ACGGTTGTTA ATTACCTGGG CGGCGAGCAC GATCTCGTCA AAGCCGTTGA  
 TGCCAACAAT TAATGGACCC GCGCTCGTG CTAGAGCAGT TTCGGCAACT  
 6201 TGTGTGGCC CACAATGTAA AGTTCCAAGA AGCGCGGGAT GCCCTTGATG  
 ACAACACCGG GTGTTACATT TCAAGGTCTT TCGCGCCCTA CGGGAACCTAC  
 6251 GAAGGCAATT TTTTAAGTTC CTCGTAGGTG AGCTCTTCAG GGGAGCTGAG  
 CTTCCGTTAA AAAATTCAAG GAGCATCCAC TCGAGAAGTC CCCTCGACTC  
 6301 CCCGTGCTCT GAAAGGGCCC AGTCTGCAAG ATGAGGGTTG GAAGCGACGA  
 GGGCACGAGA CTTTCCCGGG TCAGACGTTT TACTCCCAAC CTTGCTGCT  
 6351 ATGAGCTCCA CAGGTCACGG GCCATTAGCA TTTGCAGGTG GTCGCGAAAG  
 TACTCGAGGT GTCCAGTCCC CGGTAATCGT AAACGTCCAC CAGCGCTTTC  
 6401 GTCCTAAACT GCGACCTAT GGCCATTTT TCTGGGGTGA TGCAGTAGAA  
 CAGGATTGTA CCGCTGGATA CCGGTAAAA AGACCCCACT ACGTCATCTT  
 6451 GGTAAGCGGG TCTTGTTCCT AGCGGTCCCA TCCAAGGTTT GCGGCTAGGT  
 CCATTGCCCC AGAACAAGGG TCGCCAGGCT AGGTTCCAAG CGCCGATCCA  
 6501 CTCGCGCGGC AGTCACTAGA GGCTCATCTC CGCCGAACCT CATGACCAGC  
 GAGCGCGCCG TCAGTGATCT CCGAGTAGAG GCGGCTTGAA GTACTGGTCTG

Figure 27G

6551 ATGAAGGGCA CACTGCTT CCCAAGGCC CCCATCCAAG TATAGC  
 TACTTCCCGT GCTCGACGAA GGGTTTCCGG GGGTAGGTTT ATATCCAGAG  
 6601 TACATCGTAG GTGACAAAGA GACGCTCGGT GCGAGGATGC GAGCCGATCG  
 ATGTAGCATC CACTGTTTCT CTGCGAGCCA CGTCCCTACG CTCGGCTAGC  
 6651 GGAAGAAGTG GATCTCCCGC CACCAATTGG AGGAGTGGCT ATTGATGTGG  
 CCTTCTTGAC CTAGAGGGCG GTGGTTAACC TCCTCACC GA TAACTACACC  
 6701 TGAAAGTAGA AGTCCCTGCG ACGGGCCGAA CACTCGTGCT GGCTTTTGTA  
 ACTTTTCATCT TCAGGGACGC TGCCCGGCTT GTGAGCACGA CCGAAAACAT  
 6751 AAAACGTGCG CAGTACTGGC AGCGGTGCAC GGGCTGTACA TCCTGCACGA  
 TTTTGACGCG GTCATGACCG TCGCCACGTG CCCGACATGT AGGACGTGCT  
 6801 GGTTCGACCTG ACGACCGCGC ACAAGGAAGC AGAGTGGGAA TTTGAGCCCC  
 CCAACTGGAC TGCTGGCGCG GTTCTCTCG TCTCACCCTT AAACCTGGGG  
 6851 TCGCCTGGCG GGTTCGCTG GTGGTCTTCT ACTTCGGCTG CTTGTCTTG  
 AGCGGACCGC CCAAACCGAC CACCAGAAGA TGAAGCCGAC GAACAGGAAC  
 6901 ACCGTCTGCG TGCTCGAGGG GAGTTACGGT GGATCGGACC ACCACGCGCG  
 TGGCAGACCG ACGAGCTCCC CTCAATGCCA CCTAGCCTCG TGGTGCGGCG  
 6951 GCGAGCCCAA AGTCCAGATG TCCGCGCGCG GCGGTGGGAG CTTGATGACA  
 CGCTCGGGTT TCAGGTCTAC AGGCGCGCGC CGCCAGCCTC GAACTACTGT  
 7001 ACATCGCGCA GATGGGAGCT GTCCATGGTC TGGAGCTCCC GCGGCGTCAG  
 TGTAGCGCGT CTACCCTCGA CAGGTACCAG ACCTCGAGGG CGCCGACGTC  
 7051 GTCAGGCGGG AGCTCCTGCA GGTTCACCTC GCATAGACGG GTCAGGGCGC  
 CAGTCCGCCC TCGAGGACGT CCAAAATGGAG CGTATCTGCC CAGTCCCGCG  
 7101 GGGCTAGATC CAGGTGATAC CTAATTTCCA GGGGCTGGTT GGTGGCGGCG  
 CCCGATCTAG GTCCACTATG GATTAAAGGT CCCCACCAA CCACCGCCGC  
 7151 TCGATGGCTT GCAAGAGGCC GCATCCCCGC GCGCGACTA CGGTACCGCG  
 AGCTACCGAA CGTTCCTCCG CGTAGGGGCG CCGCGCTGAT GCCATGGCGC  
 7201 CGCGGGGCGG TGGGCGCGCG GGGTGTCTT GGATGATGCA TCTAAAAGCG  
 GCGGCGCGCC ACCCGCGCGC CCCACAGGAA CCTACTACGT AGATTTTTCG  
 7251 GTGACGCGGG CGAGCCCCCG GAGGTAGGGG GGGCTCCGGA CCCGCGGGGA  
 CACTGCGCCC GCTCGGGGGC CTCCATCCCC CCGAGGCCT GGGCGGCCCT  
 7301 GAGGGGGCAG GGGCACGTCG GCGCCGCGCG CCGGCAGGAG CTGGTGCTGC  
 CTCCCCCGTC CCCGTGCAGC CGCGGCGCGC GCGCGTCTC GACCACGACG  
 7351 GCGCGTAGGT TGCTGGCGAA CGCGACGACG CGGCGGTTGA TCTCCTGAAT  
 CGCGCATCCA ACGACCGCTT GCGCTGCTGC GCGCCCACT AGAGGACTTA  
 7401 CTGCGGCCTC TCGGTGAAGA CGACGGGCCC GGTGAGCTTG AACCTGAAAG  
 GACCGCGGAG ACGCACTTCT GCTGCCCCGG CCACTCGAAC TTGGACTTTC  
 7451 AGATTTCGAC AGAATCAATT TCGGTGTCGT TGACGGCGGC CTGGCGCAA  
 TCTCAAGCTG TCTTAGTTAA AGCCACAGCA ACTGCCGCG GACCGCGTTT

Figure 27H

7501 ATCTCCTGCA C~~CT~~CTCTGA GTTGTCTTGA TAGGCG~~TTCT~~ GGGC~~CT~~~~CT~~~~CT~~  
 TAGAGGACGT G~~CT~~GAGGACT CAACAGA~~CT~~ ATCCGCTAGA GCCCGT~~CT~~  
 7551 CTGCTCGATC TCTTCTCTCT GGAGATCTCC GCGTCCGGCT CGCTCCACGG  
 GACGAGCTAG AGAAGGAGGA CCTCTAGAGG CGCAGGCCGA GCGAGGTGCC  
 7601 TGGCGGCGAG GTCGTTGGAA ATCGGGGCCA TGAGCTGCGA GAAGGCGTTG  
 ACCGCCGCTC CAGCAACCTT TACGCCCGGT ACTCGACGCT CTTCCGCAAC  
 7651 AGGCCTCCCT CGTTCAGAC GCGGCTGTAG ACCACGCCCC CTTCCGCATC  
 TCCGGAGGGA GCAAGGTCTG CCGCGACATC TGGTGGGGG GAAGCCGTAG  
 7701 GCGGGCGCGC ATGACCACCT GCGCGAGATT GAGCTCCACG TGCCGGGCGA  
 CGCCCGCGCG TACTGGTGA GCGCTCTAA CTCGAGGTGC ACGGCCGCT  
 7751 AGACGGCGTA GTTTCGAGG CGCTGAAAGA GGTAGTTGAG GGTGGTGGCG  
 TCTGCCGCAT CAAAGCGTCC GCGACTTTCT CCATCAACTC CCACCACCGC  
 7801 GTGTGTTCTG CCACGAAGAA GTACATAACC CAGCGTCGCA ACGTGGATTC  
 CACACAAGAC GGTGCTTCTT CATGTATTGG GTCGCAGCGT TGCACCTAAG  
 7851 GTTGATATCC CCCAAGGCCT CAAGGCGCTC CATGGCCTCG TAGAAGTCCA  
 CAACTATAGG GGGTTCCGGA GTTCCGCGAG GTACCGGAGC ATCTTCAGGT  
 7901 CGGCGAAGTT GAAAACTGG GAGTTGCGCG CCGACACGGT TAACTCCTCC  
 GCCGCTTCAA CTTTTTGACC CTCAACGCGC GGCTGTGCCA ATTGAGGAGG  
 7951 TCCAGAAGAC GGATGAGCTC GGCGACAGTG TCGCGCACCT CGCGCTCAAA  
 AGGTCTTCTG CCTACTCGAG CCGCTGTCTAC AGCGCGTGA GCGCGAGTTT  
 8001 GGCTACAGGG GCCTCTTCTT CTCTTTCAAT CTCTCTTCC ATAAGGGCCT  
 CCGATGTCCC CGGAGAAGAA GAAGAAGTTA GAGGAGAAGG TATTCCCCTG  
 8051 CCCCCTCTTC TTCTTCTGGC GCGGTTGGGG GAGGGGGGAC ACGGCGGCGA  
 GGGGAAGAAG AAGAAGACCG CCGCCACCCC CTCCCCCTG TGCCGCCGCT  
 8101 CGACGGCGCA CCGGGAGGCG GTCGACAAAG CGCTCGATCA TCTCCCCGCG  
 GCTGCCGCGT GCGCCTCCGC CAGCTGTTTC GCGAGCTAGT AGAGGGGCGC  
 8151 GCGACGGCGC ATGGTCTCGG TGACGGCGCG GCCGTTCTCG CGGGGGCGCA  
 CGTGCCGCG TACCAGAGCC ACTGCCGCGC CGGCAAGAGC GCGCCGCGT  
 8201 GTTGAAGAC GCGCCCGTC ATGTCCCCTG TATGGGTTGG CGGGGGGCTG  
 CAACCTTCTG CGGCGGGCAG TACAGGGCCA ATACCAACC GCGCCCGAC  
 8251 CCATCGGCA GGGATACGGC GCTAACGATG CATCTCAACA ATTGTTGTGT  
 GGTACGCCGT CCCTATGCCG CGATTGCTAC GTAGAGTTGT TAACAACACA  
 8301 AGGTACTCCG CCGCCGAGGG ACCTGAGCGA GTCCGCATCG ACCGGATCGG  
 TCCATGAGGC GCGGCTCCC TGGACTCGCT CAGGCGTAGC TGSCCTAGCC  
 8351 AAAACCTCTC GAGAAAGCG TCTAACCACT CACAGTCGCA AGGTAGGCTG  
 TTTTGGAGAG CTCTTTCCGC AGATTGGTCA GTGTCAGCGT TCCATCCGAC  
 8401 AGCACCGTGG CGGGCGGCG GGGCGGCGG TCGGGGTTGT TTCTGGCGGA  
 TCGTGGCACC GCGCGCGTC GCGCGCGCC AGCCCCAACA AAGACCGCCT

Figure 27I

8451 GGTGCTGCTG ~~ATGTAAT~~ TAAAGTAGGC GGTCTTGAGA CGGCGG~~EG~~  
 CCACGACGAC TACTACATTA ATTTCATCCG CCAGAACTCT GCCGCC~~TACC~~  
 8501 TCGACAGAAG CACCATGTCC TTGGGTCCGG CCTGCTGAAT GCGCAGGCGG  
 AGCTGCTCTC GTGGTACAGG AACCCAGGCC GGACGACTTA CGCGTCCGCC  
 8551 TCGGCCATGC CCCAGGCTTC GTTTTGACAT CGGCGCAGGT CTTTGTAAGTA  
 AGCCGGTACG GGGTCCGAAG CAAAAGTGA GCCCGGTCCA GAAACATCAT  
 8601 GTCTTGCAAT AGCCTTTCTA CCGGCACTTC TTCTTCTCCT TCCTCTTGTC  
 CAGAAGCTAC TCGGAAAGAT GGCCGTGAAG AAGAAGAGGA AGGAGAACAG  
 8651 CTGCATCTCT TGCATCTATC GCTGCGGCGG CGGCGGAGTT TGGCCGTAGG  
 GACGTAGAGA ACGTAGATAG CGACGCCGCC GCCGCCTCAA ACCGGCATCC  
 8701 TGGCGCCCTC TTCCTCCCAT GCGTGTGACC CCGAAGCCCC TCATCGGCTG  
 ACCCGGGGAG AAGGAGGGTA CGCACACTGG GGCTTCGGGG AGTAGCCGAC  
 8751 AAGCAGGGCT AGGTCGGCGA CAACGCGCTC GGCTAATATG GCCTGCTGCA  
 TTCGTCCGA TCCAGCCGCT GTTGGCGGAG CCGATTATAC CGGACGACGT  
 8801 CCTGCGTGAG GGTAGACTGG AAGTCATCCA TGTCCACAAA GCGGTGGTAT  
 GGACGCACTC CCATCTGACC TTCAGTAGGT ACAGGTGTTT CGCCACCATA  
 8851 CGCCCGGTGT TGATGGTGTA ACTGCACTTG GCCATAACGG ACCAGTTAAC  
 CGCGGGCACA ACTACCACAT TCACGTCAAC CGGTATTGCC TGGTCAATTG  
 8901 GGTCTGGTGA CCCGGCTGCG AGAGCTCGGT GTACCTGAGA CGCGAGTAAG  
 CCAGACCACT GGGCCGACGC TCTCGAGCCA CATGGACTCT GCGCTCATTC  
 8951 CCCTCGAGTC AAATACGTAG TCGTTGCAAG TCCGCACCAG GTACTGGTAT  
 GGGAGCTCAG TTTATGCATC AGCAACGTTT AGGCGTGGTC CATGACCATA  
 9001 CCCACAAAA AGTGGCGCGG CGGCTGGCGG TAGAGGGGCC AGCGTAGGGT  
 GGGTGGTTTT TCACGCCGCC GCCGACCGCC ATCTCCCCGG TCGCATCCCA  
 9051 GGCCGGGGCT CCGGGGGCGA GATCTTCCAA CATAAGGCGA TGATATCCGT  
 CCGGCCCCGA GGCCCCCGCT CTAGAAGGTT GTATTCCGCT ACTATAGGCA  
 9101 AGATGTACCT GGACATCCAG GTGATGCCGG CGGCGGTGGT GGAGGCGCGC  
 TCTACATGGA CCTGTAGGTC CACTACGGCC GCCGCCACCA CCTCCGCGCG  
 9151 GGAAAGTCGC GGACGCGGTT CCAGATGTTG CGCAGCGGCA AAAAGTGCTC  
 CCTTTCAGCG CCTGCGCCAA GGTCTACAA CCGTCGCCGT TTTTCACGAG  
 9201 CATGGTCGGG ACGCTCTGGC CGGTCAGGCG CGCGCAATCG TTGACGCTCT  
 GTACCAGCCC TCGGAGACCG GCCAGTCCGC GCGCGTTAGC AACTGCGAGA  
 9251 AGACCGTGCA AAAGGAGAGC CTGTAAGCGG GCACTCTTCC GTGGTCTGGT  
 TCTGGCACGT TTTCTCTCTG GACATTGCGC CGTGAGAAGG CACCAGACCA  
 9301 GGATAAATTC GCAAGGGTAT CATGGCGGAC GACCGGGGTT CGAGCCCCGT  
 CCTATTAAAG CGTTCCCATTA GTACCGCCTG CTGGCCCCAA GCTCGGGGCA  
 9351 ATCCGGCCGT CCGCCGTGAT CCATGCGGTT ACCGCCCGCG TGTCGAACCC  
 TAGGCCGGCA GCGGCACTA GGTACGCCAA TGGCGGGCGC ACAGCTTGGG

Figure 27J

9401 AGGTGTGCGA GAGACAA CGGGGGAGTC CTCCTTTTGG CTTCCCTTGA  
 TCCACACGCT GAGTCTGTG GCCCCTCAC GAGGAAAACC GAAGGAAGGT  
 9451 GCGCGGCGCG CTGCTGCGCT AGCTTTTGTG GCCACTGGCC GCGCGCAGCG  
 CCGCGCCGCC GACGACGCGA TCGAAAAAAC CGGTGACCGG CCGCGCTCGC  
 9501 TAAGCGGTTA GGCTGGAAG CGAAAGCATT AAGTGGCTCG CTCCTGTAG  
 ATTGCCAAT CCGACCTTC GCTTTCGTAA TTCACCGAGC GAGGGACATC  
 9551 CCGGAGGGTT ATTTTCCAAG GGTGAGTCG CGGGACCCCC GGTTCGAGTC  
 GGCTTCCCA TAAAAGGTTT CCAACTCAGC GCCCTGGGGG CCAAGCTCAG  
 9601 TCGGACCGGC CGGACTGCGG CGAAGCGGGG TTTGCCTCCC CGTCATGCAA  
 AGCCTGGCCG GCCTGACGCC GCTTGCCCCC AAACGGAGGG GCAGTACGTT  
 9651 GACCCCGCTT GCAAATTCCT CCGGAAACAG GGACGAGCCC CTTTTTGTCT  
 CTGGGGCGAA CGTTTAAGGA GGCCTTTGTC CCTGCTCGGG GAAAAACGA  
 9701 TTTCCAGAT GCATCCGGTG CTGCGGAGAG TCGCCCCCCC TCCTCAGCAG  
 AAAGGGTCTA CGTAGCCAC GACGCCGTCT ACGCGGGGGG AGGAGTCGTC  
 9751 CCGCAAGAGC AAGAGCAGCG GCAGACATGC AGGGCACCCCT CCCCTCCTCC  
 GCCGTCTCG TTCTCGTCGC CGTCTGTACG TCCCGTGGGA GGGGAGGAGG  
 9801 TACCGCGTCA GGAGGGCGCA CATCCGCGGT TGACGCGGCA GCAGATGGTG  
 ATGGCGCAGT CCTCCCCGCT GTAGGCSCCA ACTGCGCCGT CGTCTACCAC  
 9851 ATTACGAACC CCGCGGCGGC CGGGCCCGGC ACTACCTGGA CTTGGAGGAG  
 TAATGCTTGG GGGCGCCGCG GCCCGGGCCG TGATGGACCT GAACCTCCTC  
 9901 GCGGAGGGCC TGGCGCGGCT AGGAGCGCCC TCTCCTGAGC GGCACCCAAG  
 CCGCTCCCCG ACCGCGCCGA TCCTCGCGGG AGAGGACTCG CCGTGGGTTC  
 9951 GGTGCAGCTG AAGCGTGATA CGCGTGAGGC GTACGTGCCG CGGCAGAACC  
 CCACGTCGAC TTCGCACTAT GCGCACTCCG CATGCACGGC GCCGTCTTGG  
 10001 TGTTCGCGA CCGCGAGGGA GAGGAGCCCG AGGAGATGCG GGATCGAAAG  
 ACAAGCGCT GCGCTCCCT CTCCTCGGGC TCCTCTACGC CCTAGCTTTC  
 10051 TTCCACGCAG GCGCGAGCT GCGGCATGGC CTGAATCGCG AGCGGTTGCT  
 AAGGTGCGTC CCGCGCTCGA CGCCGTACCG GACTTAGCGC TCGCCAACGA  
 10101 GCGCGAGGAG GACTTTGAGC CCGACGCGCG AACCGGGATT AGTCCCGCGC  
 CGCGCTCCTC CTGAAACTCG GGCTGCGCGC TTGGCCCTAA TCAGGGCGCG  
 10151 GCGCACACGT GCGGCGCGCC GACCTGGTAA CCGCATACGA GCAGACGGTG  
 CGCGTGTGCA CCGCGGCGCG CTGGACATT GCGGTATGCT CGTCTGCCAC  
 10201 AACCAGGAGA TTAACTTTCA AAAAGCTTT AACAAACCAG TCGGTACGCT  
 TTGGTCTCT AATTGAAAGT TTTTTCGAAA TTGTTGGTGC ACGCATGCGA  
 10251 TGTGGCGCGC GAGGAGGTGG CTATAGGACT GATGCATCTG TGGGACTTTG  
 ACACCGCGCG CTCCTCCACC GATATCCTGA CTACGTAGAC ACCCTGAAAC  
 10301 TAAGCGCGCT GGAGCAAAAC CCAAATAGCA AGCCGCTCAT GCGCGAGCTG  
 ATTCGCGCGA CCTCGTTTTG GGTATTATCGT TCGGCGAGTA CCGCGTCGAC

Figure 27K

10351 TTCCTTATAG TGCACAG CAGGGACAAC GAGGCATTCA GGGATGCT  
 AAGGAATATC ACGTCGTGTC GTCCCTGTTG CTCCGTAAGT CCCTACGCGA  
 10401 GCTAAACATA GTAGAGCCCG AGGGCCGCTG GCTGCTCGAT TTGATAAACA  
 CGATTGTGAT CATCTCGGCG TCCCGGCGAC CGACGAGCTA AACTATTTGT  
 10451 TCCTGCAGAG CATAGTGGTG CAGGAGCGCA GCTTGAGCCT GGCTGACAAG  
 AGGACGTCTC GTATCACCAC GTCCTCGCGT CGAACTCGGA CCGACTGTTT  
 10501 GTGGCCGCCA TCAACTATTC CATGCTTAGC CTGGGCAAGT TTTACGCCCG  
 CACCGCGCGT AGTTGATAAG GTACGAATCG GACCCGTTCA AAATGCGGGC  
 10551 CAAGATATAC CATACCCCTT ACGTTCCCAT AGACAAGGAG GTAAAGATCG  
 GTTCTATATG GTATGGGGAA TGCAAGGGTA TCTGTTCTTC CATTTCTAGC  
 10601 AGGGGTTCTA CATGCGCATG GCGCTGAAGG TGCTTACCTT GAGCGACGAC  
 TCCCAAGAT GTACGCGTAC CGCGACTTCC ACGAATGGAA CTCGCTGCTG  
 10651 CTGGGCGTTC ATCGCAACGA GCGCATCCAC AAGGCCGTGA GCGTGAGCCG  
 GACCCGCAAA TAGCGTTGCT GCGGTAGGTG TTCCGGCACT CGCACTCGGC  
 10701 GCGGCGCGAG CTCAGCGACC GCGAGCTGAT GCACAGCCTG CAAAGGGCCC  
 CGCCGCGCTC GAGTCGCTGG CGCTCGACTA CGTGTCGGAC GTTTCGCGG  
 10751 TGGCTGCCAC GGGCAGCGGC GATAGAGAGG CCGAGTCCTA CTTTGACGCG  
 ACCGACCGTG CCCGTCGCGG CTATCTCTCC GGCTCAGGAT GAAACTGCGC  
 10801 GCGCTGACC TGGCTGGGC CCCAAGCCGA CGCGCCCTGG AGGCAGCTGG  
 CCGCGACTGG ACGCGACCCG GGGTTGCGCT GCGCGGGACC TCCGTCGACC  
 10851 GCGCGGACCT GGGCTGGCGG TGCCACCCGC GCGCGCTGGC AACGTCGGCG  
 CCGGCTTGA CCCGACCGCC ACCGTGGCGG CGCGCGACCG TTGCAGCCGC  
 10901 GCGTGGAGGA ATATGACGAG GACGATGAGT ACGAGCCAGA GGACGGCGAG  
 CGACCTCTCT TATACTGCTC CTGCTACTCA TGCTCGGTCT CCTGCCGCTC  
 10951 TACTAAGCGG TGATGTTTCT GATCAGATGA TGCAAGACGC AACGGACCCG  
 ATGATTCGCC ACTACAAAGA CTAGTCTACT ACGTTCTGCG TTGCCTGGGC  
 11001 GCGGTGCGGG GGGCGCTGCA GAGCCAGCCG TCCGGCCTTA ACTCCACGGA  
 CGCCACGCCC GCGCGACGCT CTCGGTCGGC AGGCCGGAAT TGAGGTGCCT  
 11051 CGACTGGCGC CAGGTCATGG ACCGCATCAT GTCGCTGACT GCGCGCAATC  
 GCTGACCGCG GTCCAGTACC TGGCGTAGTA CAGCGACTGA CCGCGGTTAG  
 11101 CTGACGCGTT CCGGCAGCAG CCGCAGGCCA ACCGGCTCTC CGCAATTCTG  
 GACTGCGCAA GCGCGTCGTC GCGCTCCGGT TGGCCGAGAG GCGTTAAGAC  
 11151 GAAGCGGTGG TCCCGGCGCG CGCAAACCCC ACGCACGAGA AGGTGCTGGC  
 CTTTCGCCACC AGGGCCGCGC GCGTTTGGGG TCGTGCTCT TCCACGACCG  
 11201 GATCGTAAAC GCGCTGGCCG AAAACAGGGC CATCCGGCCC GACGAGGCCG  
 CTAGCATTTG CGCGACCGGC TTTTGTCCCG GTAGGCCGGG CTGCTCCGGC  
 11251 GCCTGGTCTA CGACGCGCTG CTTGAGCGCG TGGCTCGTTA CAACAGCGGC  
 CGGACCAGAT GCTGCGCGAC GAAGTCGCGC ACCGAGCAAT GTTGTCGCGG

Figure 27L

11301 AACGTGCAGA CCTGGA CCGGCTGGTG GGGGATGTGC GCGAGGCT  
 TTGCACGTCT GGTGGACCT GGCCGACCAC CCCCTACACG CGCTCCGGCA  
 11351 GCGCGACGCT GAGCGCGCGC AGCAGCAGGG CAACCTGGGC TCCATGGTTG  
 CCGCGTCGCA CTCGCGCGCG TCGTCGTCCC GTTGGACCCG AGGTACCAAC  
 11401 CACTAAACGC CTTCTGAGT ACACAGCCCG CCAACGTGCC GCGGGGACAG  
 GTGATTTGCG GAAGGACTCA TGTGTCGGGC GGTGACACGG CGCCCTGTG  
 11451 GAGGACTACA CCAACTTTGT GAGCGCACTG CGGCTAATGG TGACTGAGAC  
 CTCCTGATGT GGTGAAACA CTCGCGTGAC GCCGATTACC ACTGACTCTG  
 11501 ACCGCAAAGT GAGGTGTACC AGTCTGGGCC AGACTATTTT TTCCAGACCA  
 TGCGTTTCA CTCCACATGG TCAGACCCGG TCTGATAAAA AAGGTCTGGT  
 11551 GTAGACAAGG CTTGCAGACC GTAAACCTGA GCCAGGCTTT CAAAACTTG  
 CATCTGTTCC GGACGTCTGG CATTTGGACT CGGTCCGAAA GTTTTGAAC  
 11601 CAGGGGCTGT GGGGGGTGCG GGCTCCACA GCGGACCGCG CGACCGTGTC  
 GTCCCCGACA CCCCCACGC CCGAGGGTGT CCGCTGGCGC GCTGGCACAG  
 11651 TAGCTTGCTG ACCCCCAACT CGCGCCTGTT GCTGCTGCTA ATAGCGCCCT  
 ATCGAACGAC TCGGGTGA GCGCGGACAA CGACGACGAT TATCGCGGGA  
 11701 TCACGGACAG TGGCAGCGTG TCCCGGGACA CATACCTAGG TCACTTGCTG  
 AGTGCTGTG ACCGTCGCAC AGGGCCCTGT GTATGGATCC AGTGAACGAC  
 11751 ACACTGTACC GCGAGGCCAT AGGTCAGGCG CATGTGGACG AGCATACTTT  
 TGTGACATGG CGCTCCGGTA TCCAGTCCGC GTACACCTGC TCGTATGAAA  
 11801 CCAGGAGATT ACAAGTGTCA GCCGCGCGCT GGGGCAGGAG GACACGGGCA  
 GGTCTCTAA TGTTACAGT CCGCGCGCGA CCGCGTCTC CTGTGCCCCG  
 11851 GCCTGGAGGC AACCCTAAAC TACCTGCTGA CCAACCGGCG GCAGAAGATC  
 CGGACCTCCG TTGGGATTG ATGGACGACT GGTGGCCGC CGTCTCTAG  
 11901 CCCTCGTTGC ACAGTTTAAA CAGCGAGGAG GAGCGCATTT TGCGCTACGT  
 GGGAGCAACG TGTCAAATTT GTCGCTCCTC CTCGCGTAAA ACGCGATGCA  
 11951 GCAGCAGAGC GTGAGCCTTA ACCTGATGCG CGACGGGGTA ACGCCCAGCG  
 CGTCGTCTCG CACTCGGAAT TGGACTACGC GCTGCCCCAT TGCGGGTCGC  
 12001 TGGCGCTGGA CATGACCGCG CGCAACATGG AACC GGCGAT GTATGCCTCA  
 ACCGCGACCT GTACTGGCGC GCGTTGTACC TTGGCCCGTA CATACGGAGT  
 12051 AACC GGCGCT TTATCAACCG CCTAATGGAC TACTTGCATC GCGCGGCCGC  
 TTGGCCGGCA AATAGTTGGC GGATTACCTG ATGAACGTAG CGCGCCGGCG  
 12101 CGTGAACCCC GAGTATTTCA CCAATGCCAT CTTGAACCCG CACTGGCTAC  
 GCCTTGGGG CTCATAAAGT GGTACGGTA GAACTTGGGC GTGACCGATG  
 12151 CGCCCCCTGG TTTCTACACC GGGGGATTG AGGTGCCCCA GGGTAACGAT  
 GCGGGGGACC AAAGATGTGG CCCCTAAGC TCCACGGGCT CCCATTGCTA  
 12201 GGATTCCTCT GGGACGACAT AGACGACAGC GTGTTTTCCT CGCAACCGCA  
 CCTAAGGAGA CCCTGCTGTA TCTGCTGTG CACAAAAGGG GCGTTGGCGT

Figure 27 M

12251 GACCCTGCTA GATTGCAAC AGCGCGAGCA GGCAGAGGCG GCGCTGCTAA  
 CTGGGACGAT CTACGTTG TCGCGCTCGT CCGTCTCCGC CGCGACCTT

12301 AGGAAAGCTT CCGCAGGCCA AGCAGCTTGT CCGATCTAGG CGCTGCGGCC  
 TCCTTTTCGAA GCGCTCCGGT TCGTCGAACA GGCTAGATCC GCGACGCCGG

12351 CCGCGGTCAG ATGCTAGTAG CCCATTTCCA AGCTTGATAG GGTCTCTTAC  
 GCGGCCAGTC TACGATCATC GGGTAAAGGT TCGAACTATC CCAGAGAATG

12401 CAGCACTCGC ACCACCCGCC CGCGCCTGCT GGGCGAGGAG GAGTACCTAA  
 GTCGTGAGCG TGGTGGGCGG GCGCGGACGA CCGCTCCTC CTCATGGATT

12451 ACAACTCGCT GCTGCAGCCG CAGCGCGAAA AAAACCTGCC TCCGGCATTT  
 TGTGAGCGA CGACGTCGGC GTCGCGCTTT TTTTGGACGG AGGCCGTAAA

12501 CCCAACAAACG GGATAGAGAG CCTAGTGGAC AAGATGAGTA GATGGAAGAC  
 GGGTTGTTC CCTATCTCTC GGATCACCTG TTCTACTCAT CTACCTTCTG

12551 GTACGCGCAG GAGCACAGGG ACCTGCCAGG CCCGCGCCCG CCCACCCGTC  
 CATGCGCGTC CTCGTGTCCC TGCACGCTCC GGGCGCGGGC GGGTGGGCAG

12601 GTCAAAGGCA CGACCGTCAG CGGGGTCTGG TGTGGGAGGA CGATGACTCG  
 CAGTTTCCGT GCTGGCAGTC GCGCCAGACC ACACCTCCT GCTACTGAGC

12651 GCAGACGACA GCAGCGTCCT GGATTGGGA GGGAGTGGCA ACCCGTTTGC  
 CGTCTGCTGT CGTCGCAGGA CCTAAACCTT CCCTCACCGT TGGGCAAACG

12701 GCACCTTCGC CCCAGGCTGG GGAGAAATGT TTAACAAAAA AAAAAGCATG  
 CGTGAAGCG GGGTCCGACC CCTCTTACAA AATTTTTTTT TTTTTCGTAC

12751 ATGCAAAATA AAAAATCAC CAAGGCCATG GCACCGAGCG TTGGTTTCT  
 TACGTTTAT TTTTGTAGTG GTTCCGCTAC CGTGGCTCGC AACCAAAAGA

12801 TGTATTCCCC TTAGTATGCG GCGCGCGGCG ATGTATGAGG AAGGTCTCTC  
 ACATAAGGGG AATCATACGC CGCGCGCCGC TACATACTCC TTCCAGGAGG

12851 TCCCTCTAC GAGAGTGTGG TGAGCGCGGC GCCAGTGGCG GCGGCGCTGG  
 AGGGAGGATG CTCTCACACC ACTCGCGCCG CCGTCACCGC CGCCGCGACC

12901 GTTCTCCCTT CGATGCTCCC CTGGACCCGC CGTTTGTGCC TCCGCGGTAC  
 CAAGAGGGAA GCTACGAGGG GACCTGGGCG GCAAACACGG AGGCGCCATG

12951 CTGCGGCCTA CCGGGGGGAG AAACAGCATC CGTTACTCTG AGTTGGCACC  
 GACGCCGGAT GGCCCCCTC TTTGTCTAG GCAATGAGAC TCAACCGTGG

13001 CCTATTGAC ACCACCCGTG TGTACCTGGT GGACAACAAG TCAACGGATG  
 GGATAAGCTG TGGTGGGCAC ACATGGACCA CCTGTTGTTT AGTTGCCTAC

13051 TGGCATCCCT GAACTACCAG AACGACCACA GCAACTTTCT GACCACGGTC  
 ACCGTAGGGA CTTGATGGTC TTGCTGGTGT CGTTGAAAGA CTGGTGCCAG

13101 ATTCAAACA ATGACTACAG CCCGGGGGAG GCAAGCACAC AGACCATCAA  
 TAAGTTTTGT TACTGATGTC GGGCCCCCTC CGTTCTGTGT TCTGGTAGTT

13151 TCTTGACGAC CCGTCGCACT GGGGCGGCGA CCTGAAAACC ATCCTGCATA  
 AGAACTGCTG GCCAGCGTGA CCGCGCCGCT GGACTTTTGG TAGGACGTAT

Figure 27N

13201 CCAACATGCC AATGTGAAC GAGTTCATGT TTACCAATAA GTTATGCG  
 GGTGTACGG TCACTTG CTCAAGTACA AATGTTATT CAAATTTC  
 13251 CGGGTGATGG TGTGCGGCTT GCCTACTAAG GACAATCAGG TGGAGCTGAA  
 GCCCACTACC ACAGCGCGAA CGGATGATTC CTGTTAGTCC ACCTCGACTT  
 13301 ATACGAGTGG GTGGAGTTCA CGCTGCCCCG GGGCAACTAC TCCGAGACCA  
 TATGCTCACC CACCTCAAGT GCGACGGGCT CCCGTGATG AGGCTCTGGT  
 13351 TGACCATAGA CCTTATGAAC AACGCGATCG TGGAGCACTA CTTGAAAGTG  
 ACTGGTATCT GGAATACTTG TTGCGCTAGC ACCTCGTGAT GAACTTTCAC  
 13401 GGCAGACAGA ACGGGGTCTT GGAAAGCGAC ATCGGGGTAA AGTTTGACAC  
 CCGTCTGTCT TGCCCCAAGA CCTTTCGCTG TAGCCCCATT TCAAAGTGTG  
 13451 CCGCAACTTC AGACTGGGGT TTGACCCCGT CACTGGTCTT GTCATGCCTG  
 GCGGTTGAAG TCTGACCCCA AACTGGGGCA GTGACCAGAA CAGTACGGAC  
 13501 GGGTATATAC AAACGAAGCC TTCCATCCAG ACATCATTTT GCTGCCAGGA  
 CCCATATATG TTTGCTTCGG AAGGTAGGTC TGTAAGTAAA CGACGGTCCT  
 13551 TGCGGGGTGG ACTTCACCCA CAGCCGCTG AGCAACTTGT TGGCATCCG  
 ACGCCCCACC TGAAGTGGGT GTCGCGGAC TC GTTGAACA ACCCGTAGGC  
 13601 CAACCGGCAA CCCTTCCAGG AGGGCTTTAG GATCACCTAC GATGATCTGG  
 GTTCGCGGTT GGGGAAGTCC TCCCGAAATC CTAGTGGATG CTACTAGACC  
 13651 AGGGTGGTAA CATTCCCGCA CTGTTGGATG TGGACGCTA CCAGGCGAGC  
 TCCCAACATT GTAAGGGCGT GACAACCTAC ACCTGCGGAT GGTCCGCTCG  
 13701 TTGAAAGATG ACACCGAACA GGGCGGGGGT GCGGCAGGCG GCAGCAACAG  
 AACTTTCTAC TGTGGCTTGT CCCGCCCCCA CCGCGTCCGC CGTCGTTGTC  
 13751 CAGTGGCAGC GCGCGGAAG AGAACTCCA CCGGCGAGCC GCGCAATGC  
 GTCACCGTCG CCGCGCCTTC TCTTGAGGTT GCGCGGTCGG CGCCGTTACG  
 13801 AGCCGGTGGA GGACATGAAC GATCATGCCA TTCGCGGCGA CACCTTTGCC  
 TCGGCCACCT CCTGTACTTG CTAGTACGGT AAGCGCCGCT GTGGAAACGG  
 13851 ACACGGGCTG AGGAGAAGCG CGCTGAGGCC GAAGCAGCGG CCGAAGCTGC  
 TGTGCCCCGAC TCCTCTTCGC GCGACTCCGG CTTCTGCGCC GGCTTCGACG  
 13901 CGCCCCCGCT GCGCAACCCG AGGTCGAGAA GCCTCAGAAG AAACCGGTGA  
 GCGGGGGCGA CGCGTTGGGC TCCAGCTCTT CGGAGTCTTC TTGCGCCACT  
 13951 TCRAACCCCT GACAGAGGAC AGCAAGAAAC GCAGTTACAA CCTAATAAGC  
 AGTTTGGGGA CTGTCTCCTG TCGTTCCTTG CGTCAATGTT GGATTATTCG  
 14001 AATGACAGCA CCTTCACCCA GTACCGCAGC TGGTACCTTG CATACAACTA  
 TTACTGTCGT GGAAGTGGGT CATGGCGTCG ACCATGGAAC GTATGTTGAT  
 14051 CGGCGACCCCT CAGACCGGAA TCCGCTCATG GACCCTGCTT TGCCTCCTG  
 GCGGCTGGGA GTCTGSCCTT AGGCGAGTAC CTGGGACGAA ACCTGAGGAC  
 14101 ACGTAACCTG CGGCTCGGAG CAGGTCTACT GGTGCTTGCC AGACATGATG  
 TGCATTGGAC GCGGAGCCTC GTCCAGATGA CCAGCAACGG TCTGTACTAC

Figure 270

14151 CAAGACCCCG TTTTCCG CTCCACGCGC CAGATCAGCA ACTTTCCTT  
 GTTCTGGGGC ACTGGAAGGC GAGGTGCGCG GTCTAGTCGT TGAAGGCA  
 14201 GGTGGGCGCC GAGCTGTTGC CCGTGCACTC CAAGAGCTTC TACAACGACC  
 CCACCCGCGG CTCGACRACG GGCACGTGAG GTTCTCGAAG ATGTTGCTGG  
 14251 AGGCGGTCTA CTCCCACTC ATCCGCCAGT TTACCTCTCT GACCCACGTG  
 TCCGACAGAT GAGGGTTGAG TAGGCGCTCA AATGGAGAGA CTGGGTGCAC  
 14301 TTCAATCGCT TTCCCGAGAA CCAGATTTTG GCGCGCCCGC CAGCCCCCAC  
 AAGTTAGCGA AAGGGCTCTT GGTCTAAAAC CCGCGGGCGG GTCGGGGGTG  
 14351 CATCACCACC GTCAGTGAAA ACGTTCTGTC TCTCACAGAT CACGGGACGC  
 GTAGTGGTGG CAGTCACTTT TGCAAGGACG AGAGTGTCTA GTGCCCTGCG  
 14401 TACCCTGCGC CAACAGCATC GGAGGAGTCC ACCGAGTGAC CATTACTGAC  
 ATGGCGACGC GTTGTCTGAG CCTCCTCAGG TCGCTCACTG GTAATGACTG  
 14451 GCCAGACGCC GCACCTGCCC CTACGTTTAC AAGGCCCTGG GCATAGTCTC  
 CGGTCTGCGG CGTGGACGGG GATGCAAATG TTCCGGGACC CGTATCAGAG  
 14501 GCCGCGCGTC CTATCGAGCC GCACTTTTTG AGCAAGCATG TCCATCCTTA  
 CGGCGCGCAG GATAGCTCGG CGTGAAAAC TCGTTCTGAC AGGTAGGAAT  
 14551 TATCGCCCGC CAATAACACA GGCTGGGGCC TCGGTTTCCC AAGCAAGATG  
 ATAGCGGGTC GTTATTGTGT CCGACCCCGG ACGCSAAGGG TTCGTTCTAC  
 14601 TTTGGCGGGG CCAAGAAGCG CTCCGACCAA CACCCAGTGC GCGTGCGCGG  
 AAACCGCCCC GGTCTTTCGC GAGGCTGGET GTGGGTCACG CGCACGCGCC  
 14651 GCACTACCGC GCGCCCTGGG GCGCGCACA ACGCGGCGGC ACTGGGCGCA  
 CGTGATGGCG CCGGGGACCC CGCGCTGTT TCGCGCGCGG TGACCCCGCT  
 14701 CCACCGTCGA TGACGCCATC GACCGCGTGG TGGAGGAGGC GCGCAACTAC  
 GGTGGCAGCT ACTGCGGTAG CTGCGCCACC ACCTCCTCCG CGCGTTGATG  
 14751 ACGCCACGC CGCCACCAGT GTCCACAGTG GACGCGGCCA TTCAGACCGT  
 TCGGGGTGCG GCGGTGCTCA CAGGTGTAC CTGCGCCGGT AAGTCTGGCA  
 14801 GGTGCGCGGA GCCCGGCGCT ATGCTAAAAT GAAGAGACGG CGGAGGCGCG  
 CCACGCGCCT CGGGCCGCGA TACGATTTTA CTTCTCTGCC GCCTCCGCGC  
 14851 TAGCACGTGG CCACCGCCGC CGACCCGSCA CTGCCGCCCA ACGCGCGGCG  
 ATCGTGCAGC GGTGGCGGCG GCTGGGCGGT GACGCGGGT TCGCGCGCGC  
 14901 GCGGCCCTGC TTAACCGCGC ACGTCGCACC GCGCGACGGG CGGCCATGCG  
 CGCGGGGACG AATTGGCGCG TGCAGCGTGG CCGGCTGCCG GCCGGTACGC  
 14951 GCGCGCTCGA AGGCTGGCCG CGGGTATTGT CACTGTGCCC CCCAGGTCCA  
 CCGGCGAGCT TCCGACCGGC GCCCATAACA GTGACACGGG GGGTCCAGGT  
 15001 GCGGACGAGC GCGCGCGCA GCAGCGCGCG CCATTAGTGC TATGACTCAG  
 CCCTGCTCG CCGGCGGCGT CGTCGGCGCC GGTAAATCAG ATACTGAGTC  
 15051 GGTGCGAGGG GCAACGTGTA TTGGGTGCGC GACTCGGTTA GCGGCCTGCG  
 CCAGCGTCCC CGTTGCACAT AACCCACGCG CTGAGCCAAT CGCCGACGC

Figure 27P

15101 CGTCCCCGTG CCCCCCGCC CCCCCGCGCA CTAGATTGCA AGAAAAAT  
 GCACGGGCAC GCGGGGCGG GGGGCGCGTT GATCTAACGT TCTTTTCA  
 15151 ACTTAGACTC GTACTGTTGT ATGTATCCAG CGGCGGCGGC GCCTAACGAA  
 TGAATCTGAG CATGACAACA TACATAGGTC GCCGCCGCCG CGCGTTGCTT  
 15201 GCTATGTCCA ACGCAAAAT CAAAGAAGAG ATGCTCCAGG TCATCGCGCC  
 CGATACAGGT TCGCGTTTGA GTTCTTCTC TACGAGGTCC AGTAGCGCGG  
 15251 GGAGATCTAT GCGCCCCGA AGAAGGAAGA GCAGGATTAC AAGCCCCGAA  
 CCTCTAGATA CCGGGGGGCT TCTTCTTCT CGTCTAATG TTCGGGGCTT  
 15301 AGCTAAAGCG GGTCAAAAAG AAAAAGAAAG ATGATGATGA TGAATTGAC  
 TCGATTTGCG CCAGTTTTC TTTTCTTCT TACTACTACT ACTTGAACG  
 15351 GACGAGGTGG AACTGCTGCA CGCTACCGCG CCCAGGCGAC GGGTACAGTG  
 CTGCTCCACC TTGACGACGT GCGATGGCGC GGGTCCGCTG CCCATGTCAC  
 15401 GAAAGGTGCA CGCGTAAAC GTGTTTTCG ACCCGGCACC ACCGTAGTCT  
 CTTTCCAGCT GCGCATTTTG CACAAAACGC TGGGCGTGG TGGCATCAGA  
 15451 TTACGCCCCG TGAGCGCTCC ACCCGCACCT ACAAGCGCGT GTATGATGAG  
 AATGCGGGCC ACTCGCGAGG TGGGCGTGG TGTTCGCGCA CATACTACTC  
 15501 GTGTACGCGC ACGAGGACCT GCTTGAGCAG GCCAACGAGC GCCTCGGGGA  
 CAGATGCCGC TGCTCTGGA CGAACTCGTC CGGTGCTCG CGGAGCCCTC  
 15551 GTTTGCCTAC GGAAGCGGC ATAAGGACAT GCTGGCGTTG CCGCTGGACG  
 CAAACGGATG CCTTTCGCGG TATTCTGTA CGACCGCAAC GCGGACCTGC  
 15601 AGGGCAACCC AACACCTAGC CTAAGCCCG TAACACTGCA GCAGGTGCTG  
 TCCGTTGGG TTGTGGATCG GATTTCGGGC ATTGTGACGT CGTCCACGAC  
 15651 CCGCGGCTTG CACCSTCCGA AGAAAAGCGC GGCCTAAAGC GCGACTCTGG  
 GGGCGCGAAC GTGGCAGGCT TCTTTTCGCG CCGGATTTCG CGCTCAGACC  
 15701 TGACTTGCCA CCCACCGTGC AGCTGATGGT ACCCAAGCGC CAGCGACTGG  
 ACTGAACCGT GGGTGGCAGG TCGACTACCA TGGGTTCGCG GTCGCTGACC  
 15751 AAGATGTCTT GGAAAAAATG ACCGTGGAAC CTGGGCTGGA GCGCGAGGTC  
 TTCTACAGAA CCTTTTTCAC TCGCACCTTG GACCCGACCT CCGGCTCCAG  
 15801 CGCGTGCGGC CAATCAAGCA GGTGGCGCGG GGAAGTGGCG TCGAGACCGT  
 GCGCACGCGG GTTAGTTCGT CCACCGCGGC CCTGACCCGC ACGTCTGGCA  
 15851 GGACGTTTCA ATACCCACTA CCAAGTAGCAG CAGTATTGCC ACGCCACAG  
 CCTGCAAGTC TATGGGTGAT GGTCTATCGTG GTCATAACGG TCGCGGTGTC  
 15901 AGGGCATGGA GACACAAAG TCCCCGCTTG CCTCAGCGGT GCGGGATGCC  
 TCCGTACCT CTGTGTTTC AGGGGCCAAC GGAGTCGCCA CCGCCTACGG  
 15951 GCGGTGCAGG CGGTGCTGTC GCGCGCGTCC AAGACCTCTA CGGAGGTGCA  
 CGCCACGTCC GCCAGCGAGC CCGGCGCAGG TTCTGGAGAT GCTTCCACGT  
 16001 AACGGACCCG TGGATGTTTC GCGTTTCAGC CCCCCGCGC CCGCGCGGTT  
 TTGCTGGGC ACCTACAAAG CGCAAAGTCG GGGGCGCGC GCGCGCGCA

Figure 27Q

16051 CGAGGAAGTA CCGGCGCC AGCGCGCTAC TGCCCGAATA TGCCCTAAT  
GCTCCTTCAT GCCGCGGCGG TCGCGCGATG ACGGGCTTAT ACGGGATGTA

16101 CCTTCCATTG CGCCTACCCC CGGCTATCGT GGCTACACCT ACCGCCCCAG  
GGAAGGTAAC GCGGATGGGG GCCGATAGCA CCGATGTGGA TGGCGGGGTC

16151 AAGACGAGCA ACTACCCGAC GCCGAACCAC CACTGGAACC CGCCGCCGCC  
TTCTGCTCGT TGATGGGCTG CGGCTTGGTG GTGACCTTGG GCGGCGGCGG

16201 GTCGCCGTCG CCAGCCCGTG CTGGCCCCGA TTTCCGTGCG CAGGCTGGCT  
CAGCGGCAGC GGTGCGGCAC GAECGGGGCT AAAGGCACGC GTCCACCGA

16251 CGCGAAGGAG GCAGGACCCT GGTGCTGCCA ACAGCGCGCT ACCACCCAG  
GCGCTTCCTC CGTCCTGGGA CCACGACGGT TGTCGCGCGA TGGTGGGGTC

16301 CATCGTTTAA AAGCCGGTCT TTGTGTTTCT TGCAGATATG GCCCTCACCT  
GTAGCAAATT TTCGGCCAGA AACACCAAGA ACGTCTATAC CGGGAGTGGA

16351 GCCGCTCCG TTTCCCGGTG CCGGGATTCC GAGGAAGAAT GCACCGTAGG  
CGCGGGAGGC AAAGGGCCAC GGCCCTAAGG CTCCTTCTTA CGTGGCATCC

16401 AGGGGCATGG CCGGCCACGG CCTGACGGGC GGCATGCGTC GTGCGCACCA  
TCCCCGTACC GGCCGGTGCC GGA CTGCCCCG CCGTACGCAG CACGCGTGGT

16451 CCGGCGGCGG CGCGCGTCGC ACCGTCGCAT GCGCGGCGGT ATCCTGCCCC  
GGCCGCGGCC GCGCGCAGCG TGCGAGCGTA GCGCGCGCCA TAGGACGGGG

16501 TCCTTATTCC ACTGATCGCC GCGGCGATTG GCGCCGTGCC CGGAATTGCA  
AGGAATAAGG TGACTAGCGG CGCCGCTAAC GCGGGCACGG GCCTTAACGT

16551 TCCGTGGCCT TGCAGGCGCA GAGACACTGA TTAAAAACAA GTTGCATGTG  
AGGCACCGGA ACGTCCGCGT CTCTGTGACT AATTTTGTGTT CAACGTACAC

16601 GAAAAATCAA AATAAAAAGT CTGGACTCTC ACGCTCGCTT GGTCTGTAA  
CTTTTTAGTT TTATTTTCA GACCTGAGAG TGCGAGCGAA CCAGGACATT

16651 CTATTTTGTA GAATGGAAGA CATCAACTTT GCGTCTCTGG CCCC GCGACA  
GATAAAACAT CTTACCTTCT GTAGTTGAAA CGCAGAGACC GGGGCGCTGT

16701 CCGCTCGCGC CCGTTCATGG GAAACTGGCA AGATATCGGC ACCAGCAATA  
GCCGAGCGCG GGCAAGTACC CTTTGACCGT TCTATAGCCG TGGTCGTTAT

16751 TGAGCGGTGG CGCCTTCAGC TGGGGCTGCG TGTGGAGCGG CATTAAAAAT  
ACTCGCCACC GCGGAAGTCG ACCCCGAGCG ACACCTCGCC GTAATTTTTA

16801 TTCGGTTCCA CCGTTAAGAA CTATGCGAGC AAGGCCGGA ACAGCAGCAC  
AAGCCAAGGT GGCAATTCTT GATACCGTCG TTCCGGACCT TGTCGTCGTG

16851 AGGCCAGATG CTGAGGGATA AGTTGAAAGA GCAAAATTTC CAACAAAAGG  
TCCGGTCTAC GACTCCCTAT TCAACTTCT CGTTTTAAAG GTTGTTTTCC

16901 TGGTAGATGG CCTGGCCTCT GGCATTAGCG GGGTGGTGGA CCTGGCCAAC  
ACCATCTACC GGACCGGAGA CCGTAATCGC CCCACCACCT GGACCGGTTG

16951 CAGGCAGTGC AAAATAAGAT TAACAGTAAG CTTGATCCCC GCCCTCCCGT  
GTCCGTCACG TTTTATTCTA ATTGTCATT GAACTAGGGG CGGGAGGGCA

Figure 27R

17001 AGAGGAGCCT CCGGCCG TGGAGACAGT GTCTCCAGAG GGGCGT  
 TCTCCTCGGA GGTGGCCGGC ACCTCTGTCA CAGAGGTCTC CCCGCACGSC  
 17051 AAAAGCGTCC GCGCCCCGAC AGGGAAGAAA CTCTGGTGAC GCAAATAGAC  
 TTTTCGCAGG CGCGGGGCTG TCCCTTCTTT GAGACCACTG CGTTTATCTG  
 17101 GAGCCTCCCT CGTACGAGGA GGCCTAAAG CAAGGCCTGC CCACCACCCG  
 CTCGGAGGGA GCATGCTCCT CCGTGATTC GTTCCGGACG GGTGGTGGGC  
 17151 TCCCATCGCG CCCATGGCTA CCGGAGTGCT GGGCCAGCAC ACACCCGTAA  
 AGGGTAGCGC GGGTACCGAT GGCTCACGA CCCGGTCGTG TGTGGGCATT  
 17201 CGCTGGACCT GCCTCCCCC GCCGACACCC AGCAGAAACC TGTGCTGCCA  
 GCGACCTGGA CGGAGGGGGG CGGCTGTGGG TCGTCTTTGG ACACGACGGT  
 17251 GGGCCGACCG CCGTTGTGTG AACCCGTCCT AGCCGCGCGT CCCTGCGCCG  
 CCGGGCTGGC GGCAACAACA TTGGGCAGGA TCGGCGCGCA GGCACGCGC  
 17301 CGCGCCAGC GGTCCGCGAT CGTTGCGGCC CGTAGCCAGT GGCAACTGGC  
 GCGCGGTGCG CCAGGCGCTA GCAACGCCGG GCATCGGTCA CCGTTGACCG  
 17351 AAAGCACACT GAACAGCATC GTGGGTCTGG GGGTGCAATC CTTGAAGCGC  
 TTTCTGTGTA CTGTCTGTAG CACCCAGACC CCCACGTTAG GGACTTCGCG  
 17401 CGACGATGCT TCTGATAGCT AACGTGTCGT ATCTGTGTCA TGTATGCGTC  
 GCTGTACGA AGACTATCGA TTGCACAGCA TACACACAGT ACATACGCAG  
 17451 CATGTCGCGG CCAGAGGAGC TGCTGAGCCG CCGCGCGCCC GCTTTCCAAG  
 GTACAGCGGC GGTCTCCTCG ACGACTCGGC GCGCGCGCGG CAAAGGTTT  
 17501 ATGGCTACCC CTTCGATGAT GCCGCACTGG TCTTACATGC ACATCTCGGG  
 TACCGATGGG GAAGCTACTA CGGCGTCACC AGAATGTACG TGTAGAGCCC  
 17551 CCAGGACGCC TCGGAGTACC TGAGCCCCGG GCTGGTGCAG TTTGCCCCGG  
 GGTCTGCGG AGCCTCATGG ACTCGGGGCC CGACCACGTC AAACGGGCGC  
 17601 CCACCGAGAC GTACTTCAGC CTGAATAACA AGTTTAGAAA CCCACGGTG  
 GGTGGCTCTG CATGAAGTCG GACTTATTGT TCAAATCTTT GGGGTGCCAC  
 17651 GCGCCTACGC ACCACGTGAC CACAGACCGG TCCCAGCGTT TGACGCTGCG  
 CCGGATGCG TGCTGCACTG GTGTCTGGCC AGGGTCGCAA ACTGCGACGC  
 17701 GTTCATCCCT GTGGACCGTG AGGATACTGC GTACTCGTAC AAGGCGCGGT  
 CAAGTAGGGA CACCTGGCAC TCCTATGACG CATGAGCATG TTCCGCGCCA  
 17751 TCACCCTAGC TGTGGGTGAT AACCGTGTGC TGGACATGGC TTCCACGTAC  
 AGTGGGATCG ACACCCACTA TTGGCACACG ACCTGTACCG AAGGTGCATG  
 17801 TTTGACATCC GCGGCGTGCT GGACAAGGCG CCTACTTTTA AGCCCTACTC  
 AAACGTGTAGG CGCCGCACGA CCGTCCCCG GGTGAAAT TCGGGATGAG  
 17851 TGGCACTGCC TACAACGCC TGGCTCCAA GGGTCCCCA AATCCTTGCG  
 ACCGTGACGG ATGTTGCGGG ACCGAGGGT CCCACGGGGT TTAGGAACGC  
 17901 AATGGGATGA AGCTGCTACT GCTCTTGAAA TAAACCTAGA AGAAGAGGAC  
 TTACCCTACT TCGACGATGA CGAGAACTTT ATTTGGATCT TCTTCTCCTG

Figure 275

17951 GATGACAACG AATCGAAGT AGACGAGCAA GCTGAGCAGC AAAAAA  
CTACTGTTGC TTCTGCTTCA TCTGCTCGTT CGACTCGTCG TTTTGTGAGT

18001 CGTATTTTGGG CAGGCGCCTT ATTCTGGTAT AAATATTACA AAGGAGGGTA  
GCATAAACCC GTCCGCGGAA TAAGACCATA TTTATAATGT TTCCTCCCAT

18051 TTCAAATAGG TGTCGAAGGT CAAACACCTA AATATGCCGA TAAAACATTT  
AAGTTTATCC ACAGCTTCCA GTTTGTGGAT TTATACGGCT ATTTTGTAAA

18101 CAACCTGAAC CTCAAATAGG AGAATCTCAG TGGTACGAAA CAGAAATTAA  
GTTGGACTTG GAGTTTATCC TCTTAGAGTC ACCATGCTTT GTCTTTAATT

18151 TCATGCAGCT GGGAGAGTCC TAAAAAGAC TACCCCAATG AAACCATGTT  
AGTACGTCGA CCTCTCAGG ATTTTTCCTG ATGGGGTTAC TTTGGTACAA

18201 ACGGTTTATA TGCAAAACCC ACAATGAAA ATGGAGGGCA AGGCATTCTT  
TGCCAAGTAT ACGTTTGGG TGTTTACTTT TACCTCCCGT TCCGTAAGAA

18251 GTAAAGCAAC AAAATGGAAA GCTAGAAAGT CAAGTGGAAA TGCAATTTT  
CATTTTCGTTG TTTTACCTTT CGATCTTCA GTTCACCTTT ACGTTAAAAA

18301 CTCAACTACT GAGGAGCCG CAGGCAATGG TGATAACTTG ACTCCTAAAG  
GAGTTGATGA CTCCGTCGGC GTCCGTTACC ACTATTGAAC TGAGGATTTC

18351 TGGTATTGTA CAGTGAAGAT GTAGATATAG AAACCCAGCA CACTCATATT  
ACCATAACAT GTCACTTCTA CATCTATATC TTTGGGGTCT GTGAGTATAA

18401 TCTTACATGC CCACTATTAA GGAAGGTAAC TCACGAGAAC TAATGGGCCA  
AGAATGTACG GGTGATAATT CCTTCCATTG AGTGCTCTTG ATTACCCGGT

18451 ACAATCTATG CCAACAGGC CTAATTACAT TGCTTTTAGG GACAATTTTA  
TGTTAGATAC GGGTTGTCCG GATTAATGTA ACGAAAATCC CTGTTAAAAA

18501 TTGGTCTAAT GTATTACAAC AGCACGGGTA ATATGGGTGT TCTGGCGGGC  
AACCAGATTA CATAATGTTG TCGTGCCCAT TATACCCACA AGACCGCCCG

18551 CAAGCATCGC AGTTGAATGC TGTGTAGAT TTGCAAGACA GAAACACAGA  
GTTCTAGCG TCAACTTACG ACAACATCTA AACGTTCTGT CTTTGTGTCT

18601 GCTTTCATAC CAGCTTTTGC TTGATTCCAT TGGTGATAGA ACCAGGTACT  
CGAAAGTATG GTCGAAAACG AACTAAGSTA ACCACTATCT TGGTCCATGA

18651 TTTCTATGTG GAATCAGGCT GTTGACAGCT ATGATCCAGA TGTTAGAATT  
AAAGATACAC CTTAGTCCGA CAACTGTGCA TACTAGGTCT ACAATCTTAA

18701 ATTGAAAATC ATGGAAGTGA AGATGAACTT CCAAATTACT GCTTTCCT  
TAACTTTATG TACCTTGAAT TCTACTTGAA GGTTTAATGA CGAAAGGTGA

18751 GGGAGGTGTG ATTAATACAG AGACTCTTAC CAAGGTAAAA CCTAAAACAG  
CCCTCCACAC TAATTATGTC TCTGAGAATG GTTCCATTTT GGATTTTGTG

18801 GTCAGGAAAA TGGATGGGAA AAAGATGCTA CAGAAATTTT AGATAAAAAA  
CAGTCCCTTT ACCTACCTTT TTTCTACGAT GTCTTAAAAG TCTATTTTAA

18851 GAAATAAGAG TTGGAATATA TTTTGCCATG GAAATCAATC TAAATGCCAA  
CTTTATTCTC AACCTTTATF AAAACGGTAC CTTTAGTTAG ATTTACGGTT

Figure 27T

18901 CCTGTGGAGA A TCCTGT ACTCCAACAT AGCGCTGTAT TTGCCC A  
 GGACACCTCT TTAAAGGACA TGAGGTGTGA TCGCGACATA AACGGGCTGT  
 18951 AGCTAAAGTA CAGTCCTTCC AACGTAAAAA TTTCTGATAA CCCAAACACC  
 TCGATTTCAT GTCAGGAAGG TTGCATTTTT AAAGACTATT GGGTTTGTGG  
 19001 TACGACTACA TGAACAAGCG AGTGGTGGCT CCCGGGCTAG TGGACTGCTA  
 ATGCTGATGT ACTTGTTCGC TCACCACCGA GGGCCCGATC ACCTGACGAT  
 19051 CATTAACTTT GGAGCACGCT GGTCCCTTGA CTATATGGAC AACGTCAACC  
 GTAAATTGGAA CCTCGTGC GAAGGAACT GATATACCTG TTGCAGTTGG  
 19101 CATTAAACCA CCACCGCAAT GCTGGCCTGC GCTACCGCTC AATGTTGCTG  
 GTAAATTGGT GGTGGCGTTA CGACCGGACG CGATGGCGAG TTACAACGAC  
 19151 GGCAATGGTC GCTATGTGCC CTTCCACATC CAGGTGCCTC AGAAGTTCCT  
 CCGTTACCAG CGATACACGG GAAGGTGTAG GTCCACGGAG TCTTCAAGAA  
 19201 TGCCATTAAA AACCTCCTTC TCCTGCCGGG CTCATACACC TACGAGTGGA  
 ACGGTAATTT TTGGAGGAAG AGGACGGCCC GAGTATGTGG ATGCTCACCT  
 19251 ACTTCAGGAA GGATGTTAAC ATGGTTCTGC AGAGCTCCCT AGGAAATGAC  
 TGAAGTCTTT CCTACAATTG TACCAAGACG TCTCGAGGGA TCCTTTACTG  
 19301 CTAAGGGTTG ACGGAGCCAG CATTAAAGTTT GATAGCATTT GCCTTTACGC  
 GATTCCCAAC TGCTCGGTC GTAATTCAA CTATCGTAAA CGGAAATGCG  
 19351 CACCTTCTTC CCCATGGCCC ACAACACCGC CTCCACGCTT GAGGCCATGC  
 GTGAAGAAG GGGTACCGGG TGTGTGGCG GAGGTGCGAA CTCCGGTACG  
 19401 TTAGAAACGA CACCAACGAC CAGTCCTTTA ACGACTATCT CTCGCCCGCC  
 AATCTTTGCT GTGTTGCTG GTCAGGAAAT TGCTGATAGA GAGGCGGCGG  
 19451 AACATGCTCT ACCCTATACC CGCCACGCT ACCAACGTGC CCATATCCAT  
 TTGTACGAGA TGGGATATGG GCGGTTGCGA TGCTTGACAG GGTATAGGTA  
 19501 CCCCTCCCGC AACTGGGCGG CTTTCCGCGG CTGGGCCTTC ACGCGCCTTA  
 GGGGAGGGCG TTGACCCGCC GAAAGGCGCC GACCCGGAAG TGCGCGGAAT  
 19551 AGACTAAGGA AACCCTATCA CTGGGCTCGG GCTACGACCC TTATTACACC  
 TCTGATTCTT TTGGGGTAGT GACCCGAGCC CGATGCTGGG AATAATGTGG  
 19601 TACTCTGGCT CTATACCCTA CCTAGATGGA ACCTTTTACC TCAACCACAC  
 ATGAGACCGA GATATGGGAT GGATCTACCT TGGAAAATGG AGTTGGTGTG  
 19651 CTTTAAGAAG GTGGCCATTA CTTTGAATC TTCTGTGAGC TGGCCTGGCA  
 GAAATCTTC CACCGGTAAT GGAACTGAG AAGACAGTCG ACCGGACCGT  
 19701 ATGACCGCCT GCTTACCCCC AACGAGTTTG AAATTAAGCG CTCAGTTGAC  
 TACTGGCGGA CGAATGGGGG TTGCTCAAAC TTAAATTCGC GAGTCAACTG  
 19751 GGGGAGGGTT ACAACGTTGC CCAAGTGAAC ATGACCAAAG ACTGGTTCCT  
 CCCCTCCCAA TGTTCGAACG GGTACATTG TACTGGTTTC TGACCAAGGA  
 19801 GGTACAAATG CTAGCTAACT ATAACATTGG CTACCAGGGC TTCTATATCC  
 CCATGTTTAC GATCGATTGA TATTGTAACC GATGGTCCCG AAGATATAGG

Figure 274

19851 CAGAGAGCTA C GACCGC ATGTACTCCT TCTTTAGAAA CTTCAC  
GTCTCTCGAT GTTCCTGGCG TACATGAGGA AGAAATCTTT GAAGGTCGGG

19901 ATGAGCCGTC AGGTGGTGGA TGATACTAAA TACAAGGACT ACCAACAGGT  
TACTCGGCAG TCCACCACCT ACTATGATTT ATGTTCTCTGA TGGTTGTCCA

19951 GGGCATCCTA CACCAACACA ACAACTCTGG ATTTGTTGGC TACCTTGCCC  
CCCGTAGGAT GTGGTTGTGT TGTGAGACC TAAACAACCG ATGGAACGGG

20001 CCACCATGCG CGAAGGACAG GCCTACCTG CTAACCTCCC CTATCCGCTT  
GGTGGTACGC GCTTCCTGTC CGGATGGGAC GATTGAAGGG GATAGGCGAA

20051 ATAGGCAAGA CCGCAGTTGA CAGCATTACC CAGAAAAAGT TTCTTTGCGA  
TATCCGTTCT GCGTCAACT GTCGTAATGG GTCTTTTCA AAGAAACGCT

20101 TCGCACCCCTT TGGCGCATCC CATTCTCCAG TAACTTTATG TCCATGGGCG  
AGCGTGGGAA ACCGCGTAGG GTAAGAGGTC ATTGAAATAC AGGTACCCGC

20151 CACTCACAGA CCTGGGCCAA AACCTTCTCT ACGCCAACTC CGCCACGCG  
GTGAGTGTCT GGACCCGGTT TTGGAAGAGA TCGGTTGAG GCGGGTGGCG

20201 CTAGACATGA CTTTGTAGGT GGATCCCATG GACGAGCCCA CCCTTCTTTA  
GATCTGTACT GAAAACTCCA CCTAGGGTAC CTGCTCGGGT GGAAGAAAT

20251 TGTTTTGTIT GAAGTCTTTG ACGTGGTCCG TGTGCACCAG CCGCACCGCG  
ACAAAACAAA CTTCAGAAAC TGCACCAGGC ACACGTGGTC GCGGTGGCGC

20301 GCGTCATCGA AACCGTGTAC CTGCGCACGC CCTTCTCGGC CGGCAACGCC  
CGCAGTAGCT TTGGCACATG GACGCGTGGC GGAAGAGCCG GCCGTTGCGG

20351 ACAACATAAA GAAGCAAGCA ACATCAACAA CAGCTGCCGC CATGGGCTCC  
TGTTGTATTT CTTGTTTGT TGTAGTTGTT GTGACGGCG GTACCCGAGG

20401 AGTGAGCAGG AACTGAAAGC CATTGTCAA GATCTTGGTT GTGGGCCATA  
TCACTCTGCC TTGACTTTCG GTAACAGTTT CTAGAACCAA CACCCGGTAT

20451 TTTTTTGGGC ACCTATGACA AGCGCTTTCC AGGCTTTGTT TCTCCACACA  
AAAAAACCCG TGGATACTGT TCGCGAAAGG TCCGAAACAA AGAGGTGTGT

20501 AGCTCGCCTG CGCCATAGTC AATACGGCCG GTCGCGAGAC TGGGGGCGTA  
TCGAGCGGAC GCGGTATCAG TTATGCCGGC CAGCGCTCTG ACCCCCGCAT

20551 CACTGGATGG CTTTGCCTG GAACCCGCAC TCAAAAACAT GCTACCTCTT  
GTGACCTACC GGAAACGGAC CTTGGGCGTG AGTTTTTGT CGATGGAGAA

20601 TGAGCCCTTT GCCTTTTCTG ACCAGCGACT CAAGCAGGTT TACCAGTTTG  
ACTCGGGAAA CCGAAAAGAC TGGTCGCTGA GTTCGTCAA ATGGTCAAAC

20651 AGTACGAGTC ACTCCTGCGC CGTAGCGCCA TTGCTTCTTC CCCCACCGC  
TCATGCTCAG TGAGGACCGG GCATCGCGGT AACGAAGAAG GGGGCTGGCG

20701 TGTATAACGC TGGAAAAGTC CACCCAAAGC GTACAGGGGC CCAACTCGGC  
ACATATTGCG ACCTTTTCAG GTGGGTTTCG CATGTCCCCG GGTGAGCCG

20751 CGCCTGTGGA CTATTCTGCT GCATGTTTCT CCACGCCTTT GCCAACTGGC  
CGCGACACCT GATAAGACGA CGTACAAAGA GGTGCGGAAA CGGTTGACCG

Figure 27V.

20801 CCCAACTCC C GATCAC ACCCCACCA TGAACCTTAT TACCGG A  
GGGTTTGAGG GTACCTAGTG TTGGGGTGGT ACTTGGAATA ATGCCCCCAT

20851 CCCAACTCCA TGCTCAACAG TCCCCAGGTA CAGCCCACCC TGCCTCGCAA  
GGGTTGAGGT ACGAGTTGTC AGGGGTCCAT GTCGGGTGGG ACGCAGCGTT

20901 CCAGGAACAG CTCTACAGCT TCCTGGAGCG CCACTCGCCC TACTTCCGCA  
GGTCCTTGTC GAGATGTCGA AGGACCTCGC GGTGAGCGGG ATGAAGGCGT

20951 GCCACAGTGC GCAGATTAGG AGCGCCACTT CTTTTGTCA CTTGAAAAAC  
CGGTGTCACG CGTCTAATCC TCGCGGTGAA GAAAAACAGT GAACTTTTTG

21001 ATGTAAAAAT AATGTACTAG AGACACTTTC AATAAAGSCA AATGCTTTTA  
TACATTTTTA TTACATGATC TCTGTGAAAG TTATTTCCGT TIACGAAAAAT

21051 TTTGTACACT CTCGGGTGAT TATTTACCCC CACCCTTGCC GTCTGCGCCG  
AAACATGTGA GAGCCCACTA ATAAATGGGG GTGGGAACGG CAGACGCGGG

21101 TTTAAAAATC AAAGGGGTTC TGCCGCGCAT CGCTATGCGC CACTGGCAGG  
AAATTTTTAG TTTCCCAAG ACGGCGCGTA GCGATACGCG GTGACCGTCC

21151 GACACGTTGC GATACTGGTG TTTAGTGTC CACTTAACT CAGGCACAAC  
CTGTGCAACG CTATGACCAC AAATCACGAG GTGAATTTGA GTCCGTGTTG

21201 CATCCGCGGC AGCTCGGTGA AGTTTTCACT CCACAGGCTG CGCACCATCA  
GTAGCGCGCG TCGAGCCACT TCAAAAGTGA GGTGTCCGAC GCGTGGTAGT

21251 CCAACGCGTT TAGCAGGTG GCGCCGATA TCTTGAAGTC GCAGTTGGGG  
GGTTGCGCAA ATCGTCCAGC CCGCGGCTAT AGAAGTTTCA CGTCAACCCC

21301 CCTCCGCCCT GCGCGCGCGA GTTGCATAC ACAGGGTTGC AGCACTGGAA  
GGAGCGGGGA GCGCGCGCGT CAACGCTATG TGTCCCAACG TCGTGACCTT

21351 CACTATCAGC GCCGGGTGGT GCACGCTGGC CAGCACGCTC TTGTGCGAGA  
GTGATAGTCG CGGCCACCA CGTGCGACCG GTCGTGCGAG AACAGCCTCT

21401 TCAGATCCGC GTCCAGGTCC TCCGCGTGC TCAGGGCGAA CGGAGTCAAC  
AGTCTAGGCG CAGGTCCAGG AGGCGCAACG AGTCCCGCTT GCCTCAGTTG

21451 TTTGGTAGCT GCCTTCCAA AAAGGGCGCG TGCCAGGCT TTGAGTTGCA  
AAACCATCGA CGGAAGGGT TTTCCGCGC ACGGGTCCGA AACTCAACGT

21501 CTCGCACCGT AGTGGCATCA AAAGGTGACC GTGCCCCGTC TGGGCGTTAG  
GAGCGTGGCA TCACCGTAGT TTCCACTGG CACGGGCCAG ACCCGCAATC

21551 GATACAGCGC CTGCATAAAA GCCTTGATCT GCTTAAAAGC CACCTGAGCC  
CTATGTCGCG GACGTATTTT CGGAAGTAGA CGAATTTTCG GTGGACTCGG

21601 TTTGCGCCTT CAGAGAAGAA CATGCCGCAA GACTTGCCGG AAAACTGATT  
AAACGCGGAA GTCTCTCTT GTACGGCGTT CTGAACGGCC TTTTGACTAA

21651 GGCCGGACAG GCCGCGTCGT GCACGCAGCA CCTTGCCTCG GTGTTGGAGA  
CCGGCCTGTC CGGCGCAGCA CGTGCCTCGT GGAACGCAGC CACAACCTCT

21701 TCTGCACCAC ATTTGCGCCC CACCGGTTCT TCACGATCTT GGCCTTGCTA  
AGACGTGGTG TAAAGCCGGG GTGGCCAAGA AGTCTAGAA CCGGAACGAT

Figure 27W

21751 GACTGCTCCT TCGCGCG CTGCCCGTTT TCGCTCGTCA CATUCA  
 CTGACGAGGA AGTCGCGCGC GACGGGCAAA AGCGAGCAGT GTAGGTAAAG  
 21801 AATCACGTGC TCCTTATTTA TCATAATGCT TCCGTGTAGA CACTTAAGCT  
 TTAGTGCACG AGGAATAAAT AGTATTACGA AGGCACATCT GTGAATTCEA  
 21851 CGCCTTCGAT CTCAGCGCAG CGGTGCAGCC ACAACGCGCA GCCCGTGGGC  
 GCGGAAGCTA GAGTCGCGTC GCCACGTCCG TGTTGCGCGT CGGGCACCCG  
 21901 TCGTGATGCT TGTAGGTCAC CTCTGCAAAC GACTGCAGGT ACGCCTGCAG  
 AGCACTACGA ACATCCAGTG GAGACGTTTG CTGACGTCCA TCGCGACGTC  
 21951 GAATCGCCCC ATCATCGTCA CAAAGGTCTT GTTGCTGGTG AAGGTACAGCT  
 CTTAGCGGGG TAGTAGCAGT GTTTCAGAA CAACGACCAC TTCCAGTCGA  
 22001 GCAACCCGCG GTGCTCCTCG TTCAGCCAGG TCTTGCTATC GGCCGCCAGA  
 CGTTGGGCGC CACGAGGAGC AAGTCGGTCC AGAACGTATG CCGCGCGTCT  
 22051 GCTTCCACTT GGTGAGGAG TAGTTTGAAG TTCGCTTTA GATCGTTATC  
 CGAAGGTGAA CCAGTCCGTC ATCAAACCTC AAGCGGAAAT CTAGCAATAG  
 22101 CACGTGGTAC TTGTCCATCA GCGCGCGCGC AGCCTCCATG CCCTTCTCCC  
 GTGCACCATG AACAGGTAGT CCGCGCGCGC TCGGAGGTAC GGAAGAGGG  
 22151 ACGCAGACAC GATCGGCACA CTCAGCGGGT TCATCACCGT AATTTCACTT  
 TCGCTCTGTG CTAGCCGTGT GAGTCGCCCC AGTAGTGGCA TTAAAGTGAA  
 22201 TCCGCTTCGC TGGGCTCTTC CTCTTCTCT TCGCTCCGCA TACCACGCGC  
 AGGCGAAGCG ACCCGAGAAG GAGAAGGAGA ACGCAGGCGT ATGGTGCAGC  
 22251 CACTGGGTGC TCTTCATTCA GCGCGCGCAC TGTCGCTTA CCTCCTTTGC  
 GTGACCCAGC AGAAGTAAGT CCGCGCGCTG ACACGCGAAT GAGGAAACG  
 22301 CATGCTTGAT TAGCACCGGT GGGTTGCTGA AACCACCAT TTGTAGCGCC  
 GTACGAATA ATCGTGCCCA CCCAACGACT TTGGGTGGTA AACATCGCGG  
 22351 ACATCTTCTC TTTCTTCTC GCTGTCCACG ATTACCTCTG GTGATGGCGG  
 TGTAGAAGAG AAAGAAGGAG CGACAGGTGC TAATGGAGAC CACTACCGCC  
 22401 GCGCTCGGGC TTGGGAGAAG GCGCTTCTT TTTCTTCTTG GCGCAATGG  
 CCGGAGCCCG AACCTCTTC CCGGAAGAA AAAGAAGAAC CCGGTTACC  
 22451 CCAAATCCGC CGCCGAGGTC GATGGCCGCG GGCTGGGTGT GCGCGGCACC  
 GGTTTAGGCG GCGCTCCAG CTACCGGCGC CCGACCCACA CCGCCGTGG  
 22501 AGCGCGTCTT GTGATGAGTC TTCCTCGTCC TCGGACTCGA TACGCCGCTT  
 TCGCGCAGAA CACTACTCAG AAGGAGCAGG AGCCTGAGCT ATGCGGCGGA  
 22551 CATCCGCTTT TTTGGGGGCG CCCGGGGAGG CGGCGGCGAC GGGGACGGG  
 GTAGGCGAAA AAACCCCGC GGGCCCTCC GCGCGCGTG CCCCTGCCCC  
 22601 ACGACACGTC CTCCATGGT GGGGGACGTC GCGCCGCACC GCGTCCGCGC  
 TGCTGTGAG GAGGTACCAA CCCCTGCGAG CCGGGCGTGG CGCAGGCGCG  
 22651 TCGGGGGTGG TTTGCGGCTG CTCCTCTTCC CGACTGGCCA TTTCTTCTC  
 AGCCCCCACC AAAGCGCGAC GAGGAGAAGG GCTGACCGGT AAAGGAAGAG

Figure 27 X

22701 CTATAGGCAG AAGATCA TGGAGTCAGT CGAGAAGAAG GACAGC  
GATATCCGTC TTTTCTAGT ACCTCAGTCA GCTCTTCTTC CTGTCCGATT

22751 CCGCCCCCTC TGAGTTCGCC ACCACCGCCT CCACCGATGC CGCCAACGCG  
GGCGGGGGAG ACTCAAGCGG TGGTGGCGGA GGTGGCTACG GCGGTTGCGC

22801 CCTACCACCT TCCCCGTCGA GGCACCCCGG CTTGAGGAGG AGGAAGTGAT  
GGATGGTGGA AGGGGCAGCT CCGTGGGGGC GAACTCCTCC TCCTTCACTA

22851 TATCGAGCAG GACCCAGGTT TTGTAAGCGA AGACGACGAG GACCGCTCAG  
ATAGCTCGTC CTGGGTCCAA AACATTGCT TCTGCTGCTC CTGGCGAGTC

22901 TACCAACAGA GGATAAAAAG CAAGACCAGG ACAACGCAGA GGCAAACGAG  
ATGGTTGTCT CTTATTTTTC GTTCTGGTCC TGTTCGCTCT CCGTTTGCTC

22951 GAACAAGTCG GCGGGGGGGA CGAAGGCAT GCGGACTACC TAGATGTGGG  
CTGTTCAGC CCGCCCCCTC GCTTCCGTA CCGCTGATGG ATCTACACCC

23001 AGACGACGTG CTGTTGAAGC ATCTGCAGCG CCAGTGCGCC ATTATCTGCG  
TCTGCTGCAC GACAACCTCG TAGACGTCGC GGTACGCGG TAATAGACGC

23051 ACGCGTTGCA AGAGCGCAGC GATGTGCCCC TCGCCATAGC GGATGTCAGC  
TGCAGAACGT TCTGCGCTCG CTACACGGGG AGCGGTATCG CCTACAGTCG

23101 CTTGCCTACG AACGCCACCT ATTCTCACC GCGGTACCCC CCAAACGCCA  
GAACGGATGC TTGCGGTGGA TAAGAGTGGC GCGCATGGGG GGTTCGCGT

23151 AGAAAACGGC ACATGCGAGC CCAACCCGCG CCTCAACTTC TACCCCGTAT  
TCTTTTGCCG TGTACGCTCG GGTGGGCGC GGAGTGAAG ATGGGGCATA

23201 TTGCCGTGCC AGAGGTGCTT GCCACCTATC ACATCTTTTT CCAAACTGC  
AACGGCACGG TCTCCACGAA CCGTGGATAG TGTAGAAAAA GGTTCGACG

23251 AAGATACCCC TATCCTGCCG TGCCAACCGC AGCCGAGCGG ACAAGCAGCT  
TTCTATGGGG ATAGGACGGC ACGGTGGCG TCGGCTCGCC GTTTCGTCGA

23301 GGCCCTGCGG CAGGGCGCTG TCATACCTGA TATCGCCTCG CTCAACGAAG  
CCGGAACGCC GTCCCGCGAC AGTATGGACT ATAGCGGAGC GAGTTGCTTC

23351 TGCCAAAAAT CTTTGAGGGT CTTGGACGCG ACGAGAAGCG GCGGGCAAAC  
ACGGTTTTTA GAAACTCCCA GAACCTGCGC TGCTCTTCGC GCGCCGTTTG

23401 GCTCTGCAAC AGGAAAACAG CGAAAATGAA AGTCACTCTG GAGTGTGGT  
CGAGACGTTG TCCTTTTGTG GCTTTTACTT TCAGTGAGAC CTCACAACCA

23451 GGAACCTGAG GGTGACAACG CGCGCCTAGC CGTACTAAAA CGCAGCATCG  
CCTTGAGCTC CCACTGTTGC GCGCGGATCG GCATGATTTT GCGTCGTAGC

23501 AGGTCACCCA CTTTGCCTAC CCGGCACTTA ACCTACCCCC CAAGGTCATG  
TCCAGTGGGT GAAACGGATG GGCCGTGAAT TGGATGGGG GTTCCAGTAC

23551 AGCACAGTCA TGAGTGAGCT GATCGTGCGC CGTGCGCAGC CCCTGGAGAG  
TCGTGTCACT ACTCACTCGA CTAGCACGCG GCACGCGTCG GGGACCTCTC

23601 GGATGCAAAAT TTGCAAGAAC AAACAGAGGA GGGCCTACCC GCAGTTGGCG  
CCTACGTTTA AACGTTCTTG TTTGTCTCCT CCGGATGGG CGTCAACCGC

Figure 27 Y

23651 ACGAGCAGCT ACGCTGG CTTCAAACGC GCGAGCCTGC CGACTT G  
TGCTCGTCGA TCGCGCGACC GAAGTTTGGC CGCTCGGACG GCTGAACCTC

23701 GAGCGACGCA AACTAATGAT GGCCGCAGTG CTCGTTACCG TGGAGCTTGA  
CTCGCTGCGT TGTATTACTA CCGGCCTCAC GAGCAATGGC ACCTCGAACT

23751 GTGCATGCAG CGGTTCTTTG CTGACCCGGA GATGCAGCGC AAGCTAGAGG  
CACGTACGTC GCCAAGAAAC GACTGGGCCT CTACGTCCGC TTCGATCTCC

23801 AAACATTGCA CTACACCTTT CGACAGGGCT ACGTACGCCA GGCCTGCAAG  
TTTGTAAAGT GATGTGAAA GCTGTCCCGA TGCATGCGGT CCGGACGTTT

23851 ATCTCCAACG TGGAGCTCTG CAACCTGGTC TCCTACCTTG GAATTTTGCA  
TAGAGGTTGC ACCTCGAGAC GTTGGACCAG AGGATGGAAC CTTAAAACGT

23901 CGAAAACCGC CTTGGGCAAA ACGTGCTTCA TTCCACGCTC AAGGGCGAGG  
GCTTTTGGCG GAACCCGTTT TGCACGAAGT AAGGTGCGAG TTCCCGCTCC

23951 CGCGCCGCGA CTACGTCCGC GACTGCGTTT ACTTATTTCT ATGCTACACC  
GCGCGGCGCT GATGCAGGCG CTGACGCAAA TGAATAAAGA TACGATGTGG

24001 TGGCAGACGG CCATGGGCGT TTGGCAGCAG TGCTTGGAGG AGTGCAACCT  
ACCGTCTGCC GGTACCCGCA AACCGTCGTC ACGAACCTCC TCACGTTGGA

24051 CAAGGAGCTG CAGAACTGC TAAAGCAAAA CTTGAAGGAC CTATGGACGG  
GTTCTCGAC GTCTTTGACG ATTTGTTTTT GAACTTCTCG GATACCTGCC

24101 CCTTCAACGA GCGCTCCGTG GCCGCGCACC TGGCGGACAT CATTTTCCCC  
GGAAGTTGCT CCGGAGGCAC CGCGCGGTGG ACCGCTGTA GTAAAAGGGG

24151 GAACGCCTGC TTAACACCTT GCAACAGGGT CTGCCAGACT TCACCAGTCA  
CTTGCGGACG AATTTTGGGA CGTTGTCCCA GACGGTCTGA AGTGGTCAGT

24201 AAGCATGTTG CAGAACTTTA GGAACCTTAT CCTAGAGCGC TCAGGAATCT  
TTCGTACAAC GTCTTGAAAT CCTTGAAATA GGATCTCGCG AGTCCTTAGA

24251 TGCCCGCCAC CTGCTGTGCA CTTCTTAGCG ACTTTGTGCC CATTAGTAC  
ACGGGCGGTG GACGACACGT GAAGGATCGC TGAAACACGG GTAATTCTATG

24301 CGCGAATGCC CTCCGCCGCT TTGGGGCCAC TGCTACCTTC TGCAGCTAGC  
GCGCTTACGG GAGGCGGCGA AACCCCGGTG ACGATGGAAG ACGTCGATCG

24351 CAACTACCTT GCCTACCACT CTGACATAAT GGAAGACGTG AGCGGTGACG  
GTTGATGGAA CGGATGGTGA GACTGTATTA CCTTCTGCAC TCGCCACTGC

24401 GTCTACTGGA GTGTCACGTG CGCTGCAACC TATGCACCCC GCACCGCTCC  
CAGATGACCT CACAGTGACA GCGACGTGG ATACGTGGGG CGTGGCGAGG

24451 CTGGTTTGCA ATTGCGAGCT GCTTAACGAA AGTCAAATTA TCGGTACCTT  
GACCAAACGT TAAGCGTCGA CGAATTGCTT TCAGTTTAAT AGCCATGGAA

24501 TGAGCTGCAG GGTCCCTCGC CTGACGAAAA GTCCGCGGCT CCGGGGTGA  
ACTCGACGTC CCAGGGAGCG GACTGCTTTT CAGGCGCCGA GGCCCCAACT

24551 AACTACTTCC GGGGCTGTGG ACGTCGGCTT ACCTTCGCAA ATTTGTACCT  
TTGAGTGAGG CCCCACACC TGCAGCCGAA TGGAAGCGTT TAAACATGGA

Figure 272

24601 GAGGACTACC AC~~CC~~CCACGA GATTAGGTTT TACGAAGACC AATCCC~~CC~~CC  
 CTCCTGATGG TCGGGGTGCT CTAATCCAAG ATGCTTCTGG TTAGGGCGGG  
 24651 GCCTAATGCG GAGCTTACCG CCTGCGTCAT TACCCAGGGC CACATTCTTG  
 CGGATTACGC CTCGAATGGC GGACGCAGTA ATGGGTCCCG GTGTAAGAAG  
 24701 GCCAATTGCA AGCCATCAAC AAAGCCCGCC AAGAGTTTCT GCTACGAAAG  
 CGGTTAACGT TCGGTAGTTG TTTCGGGCGG TTCTCAAAGA CGATGCTTTC  
 24751 GGACGGGGGG TTTACTTGGA CCCCAGTCC GGCGAGGAGC TCAACCCAAT  
 CCTGCCCCC AAATGAACCT GGGGGTCAGG CCGCTCCTCG AGTTGGGTTA  
 24801 CCCCCCGCCG CCGCAGCCCT ATCAGCAGCA GCCGCGGGCC CTTGCTTCCC  
 GGGGGGCGGC GCGTCGCGGA TAGTCGTCTGT CCGCGCCCGG GAACGAAGGG  
 24851 AGGATGGCAC CCAAAAAGAA GCTGCAGCTG CCGCCGCCAC CCACGGACGA  
 TCCTACCGTG GGTTTTCTT CGACGTCGAC GGCGGCGGTG GGTGCTGCT  
 24901 GGAGGAATAC TGGGACAGTC AGGCAGAGGA GGTTTTGGAC GAGGAGGAGG  
 CCTCCTATG ACCCTGTGAG TCCGTCTCCT CCAAAACCTG CTCCTCCTCC  
 24951 AGGACATGAT GGAAGACTGG GAGAGCCTAG ACGAGGAAGC TTCCGAGGTC  
 TCCTGTACTA CCTTCTGACC CTCTCGGATC TGCTCCTTCG AAGGCTCCAG  
 25001 GAAGAGGTGT CAGACGAAAC ACCGTCACCC TCGGTGCGAT TCCCTCGCC  
 CTTCTCCACA GTCTGCTTTG TGGCAGTGGG AGCCAGCGTA AGGGGAGCGG  
 25051 GGCGCCCCAG AAATCGGCAA CCGGTTCCAG CATGGCTACA ACCTCCGCTC  
 CCGCGGGGTC TTTAGCCGTT GGCCAAGGTC GTACCGATGT TGGAGGCGAG  
 25101 CTCAGGCGCC GCCGGCACTG CCCGTTGCGC GACCCAACCG TAGATGGGAC  
 GAGTCCGCGG CGGCCGTGAC GGGCAAGCGG CTGGGTGGC ATCTACCCTG  
 25151 ACCACTGGAA CCAGGGCCCG TAAGTCCAAG CAGCCGCCGC CGTTAGCCCA  
 TGGTGACCTT GGTCCCGGCC ATTCAAGGTC GTCGGCGGCG GCAATCGGGT  
 25201 AGAGCAACAA CAGCGCCAAG GCTACCGCTC ATGGCGCGGG CACAAGAAGC  
 TCTCGTTGTT GTCCGGGTTT CGATGGCGAG TACCGCGCCC GTGTTCTTGC  
 25251 CCATAGTTGC TTGCTTGCAA GACTGTGGGG GCAACATCTC CTTGCCCCGC  
 GGTATCAACG AACGAACGTT CTGACACCCC CGTTGTAGAG GAAGCGGGCG  
 25301 CGCTTTCTTC TCTACCATCA CGGCGTGGCC TTCCCCGTA ACATCCTGCA  
 CGGAAAGAAG AGATGGTAGT GCCGCACCGG AAGGGGGCAT TGTAGGACGT  
 25351 TTAATACCGT CATCTCTACA GCCCATACTG CACCGGCGGC AGCGGCAGCA  
 AATGATGGCA GTAGAGATGT CCGGTATGAC GTGGCCCGCG TCGCGCTCGT  
 25401 ACAGCAGCGG CCACACAGAA GCAAAGGCGA CCGGATAGCA AGACTCTGAC  
 TGTGTCGCC GGTGTGTCTT CGTTTCCGCT GGCTATCGT TCTGAGACTG  
 25451 AAAGCCCAAG AAATCCACAG CGCGGCGAGC AGCAGGAGGA GGAGCGCTGC  
 TTTCCGGGTC TTTAGGTGTC GCCGCGGTCG TCGTCTCCTT CCTCGCGACG  
 25501 GTCTGGCGCC CAACGAACCC GTATCGACCC GCGAGCTTAG AAACAGGATT  
 CAGACCCCGG GTTGTCTGGG CATAGCTGGG CGCTCGAATC TTTGTCTTAA

Figure 27 AA

25551 TTTCCCACTC TGCTAT ATTTCAACAG AGCAGGGGCC AAGAACA  
 AAAGGGTGAG ACATACGATA TAAAGTTGTC TCGTCCCCGG TTCTTGTTCT  
 25601 GCTGAAAATA AAAACAGGT CTCTGCGATC CCTCACCCGC AGCTGCCTGT  
 CGACTTTTAT TTTTGTCCA GAGACGCTAG GGAGTGGGCG TCGACGACA  
 25651 ATCACAAAAG CGAAGATCAG CTTGCGCGCA CGCTGGAAGA CGCGGAGGCT  
 TAGTGTTTTC GCTTCTAGTC GAAGCCGCGT GCGACCTTCT GCGCCTCCGA  
 25701 CTCTTCAGTA AATACTGCGC GCTGACTCTT AAGGACTAGT TTCGCGCCCT  
 GAGAAGTCAT TTATGACGCG CGACTGAGAA TTCTGATCA AAGCGCGGGA  
 25751 TTCTCAAATT TAAGCGCGAA AACTACGTCA TCTCCAGCGG CCACACCCGG  
 AAGAGTTTAA ATTGCGCCTT TTGATGCACT AGAGGTGCGC GGTGTGGGCC  
 25801 CGCCAGCACC TGTGTGTCAGC GCCATTATGA GCAAGGAAAT TCCCACGCCC  
 GCGGTCTGTG ACAACAGTCG CCGTAATACT CGTTCCTTTA AGGGTGGGG  
 25851 TACATGTGGA GTTACCAGCC ACAAAATGGGA CTTGCGGCTG GAGCTGCCCA  
 ATGTACACCT CAATGGTCCG TGTTTACCCT GAACCCGAC CTCGACGGGT  
 25901 AGACTACTCA ACCCGAATAA ACTACATGAG CGCGGGACCC CACATGATAT  
 TCTGATGAGT TGGGCTTATT TGATGTACTC GCGCCTGGG GTGTACTATA  
 25951 CCCGGGTCAA CGGAATACGC GCCCACCAGAA ACCGAATTCT CCTGGAACAG  
 GGGCCAGTT GCCTTATGCG CCGGTGGCTT TGGCTTAAGA GGACCTTGTC  
 26001 GCGGCTATTA CCACCACACC TCGTAATAAC CTTAATCCCC GTAGTTGGCC  
 CGCCGATAAT GGTGGTGTGG AGCATTATG GAATTAGGGG CATCAACCGG  
 26051 CGCTGCCCTG GTGTACCAGG AAAGTCCCGC TCCCACCACT GTGGTACTTC  
 GCGACGGGAC CACATGGTCC TTTCAGGGCG AGGGTGGTGA CACCATGAAG  
 26101 CCAGAGACGC CCAGGCCGAA GTTCAGATGA CTAACTCAGG GGCGCAGCTT  
 GGTCTCTGCG GGTCCGGCTT CAAGTCTACT GATTGAGTCC CCGCGTCGAA  
 26151 GCGGGCGGCT TTCGTACAGG GGTGCGGTCG CCCGGGCAGG GTATAACTCA  
 CGCCCCCGGA AAGCAGTGTC CCACGCCAGC GGGCCCGTCC CATATTGAGT  
 26201 CCTGACAATC AGAGGGCGAG GTATTGAGCT CAACGACGAG TCGGTGAGCT  
 GGACTGTTAG TCTCCCGCTC CATAAGTCGA GTTGCTGCTC AGCCACTCGA  
 26251 CCTCGCTTGG TCTCCGTCCG GACGGGACAT TTCAGATCGG CGGCGCCGGC  
 GGAGCGAACC AGAGGCAGGC CTGCCCTGTA AAGTCTAGCC GCCGCGCCG  
 26301 CGCTCTTCAT TCACGCCTCG TCAGGCAATC CTAACCTCTG AGACCTCGTC  
 CGGAGAAGTA AGTCCGGAGC AGTCCGTTAG GATTGAGACG TCTGGAGCAG  
 26351 CTCTGAGCCG CGCTCTGGAG GCATTGGAAC TCTGCAATTT ATTGAGGAGT  
 GAGACTCGGC GCGAGACCTC CGTAACCTTG AGACGTTAAA TAACTCTCA  
 26401 TTGTGCCATC GGTCTACTTT AACCCCTTCT CGGGACCTCC CGGCCACTAT  
 AACACGGTAG CCAGATGAAA TTGGGGAAGA GCCCTGGAGG GCCGGTGATA  
 26451 CCGGATCAAT TTATTCCTAA CTTTGACGCG GTAAAGGACT CGGCGGACGG  
 GGCCTAGTTA AATAAGGATT GAAACTGCGC CATTTCTGA GCCGCTGCC

Figure 27 AB

26501 CTACGACTGA A TAAGTG GAGAGGCAGA GCAACTGCCG CTGAAA C  
 GATGCTGACT TACAATTAC CTCTCCGTCT CGTTGACGCG GACTTTGTGG  
 26551 TGGTCCACTG TCGCCGCCAC AAGTGCTTTG CCCGCGACTC CGGTGAGTTT  
 ACCAGGTGAC AGCGGCGGTG TTCACGAAAC GGGCGCTGAG GCCACTCAAA  
 26601 TGCTACTTTG AATTGCCCCG GGATCATATC GAGGGCCCCG CGCACGGCGT  
 ACGATGAAAC TTAACGGGCT CCTAGTATAG CTCCCGGGCC GCGTGCCGCA  
 26651 CCGGCTTACC GCCCAGGGAG AGCTTGCCCG TAGCCTGATT CGGGAGTTTA  
 GGCCGAATGG CGGGTCCCTC TCGAACGGGC ATCGGACTAA GCCCTCAAAT  
 26701 CCCAGCGCCC CCTGCTAGTT GAGCGGGACA GGGGACCCTG TGTCTCACT  
 GGGTCGCGGG GGACGATCAA CTCGCCCTGT CCCCTGGGAC ACAAGAGTGA  
 26751 GTGATTTGCA ACTGTCCTAA CCCTGGATTA CATCAAGATC TTTGTTGCCA  
 CACTAAACGT TGACAGGATT GGGACCTAAT GTAGTTCTAG AAACAACGGT  
 26801 TCTCTGTGCT GAGTATAATA AATACAGAAA TAAATATA CTGGGGCTCC  
 AGAGACACGA CTCATATTAT TTATGTCTTT AATTTTATAT GACCCCGAGG  
 26851 TATCGCCATC CTGTAAACGC CACCGTCTTC ACCCGCCCAA GCAAACCAAG  
 ATAGCGGTAG GACATTTGCG GTGGCAGAAG TGGGCGGGTT CGTTTGGTTC  
 26901 GCGAACCTTA CCTGGTACTT TTAACATCTC TCCCTCTGTG ATTTACAACA  
 CGCTTGGAAAT GGACCATGAA AATTGTAGAG AGGGAGACAC TAAATGTTGT  
 26951 GTTTCAACCC AGACGGAGTG AGTCTACGAG AGAACCTCTC CGAGCTCAGC  
 CAAAGTTGGG TCTGCCTCAC TCAGATGCTC TCTTGAGAG GCTCGAGTCG  
 27001 TACTCCATCA GAAAAACAC CACCCTCCTT ACCTGCCGGG AACGTACGAG  
 ATGAGGTAGT CTTTTTTGTG GTGGGAGGAA TGGACGGCCC TTGCATGCTC  
 27051 TGGCTCACCG GCCGCTGCAC CACACCTACC GCCTGACCGT AAACCAGACT  
 ACGCAGTGGC CGGCGACGTG GTGTGGATGG CGGACTGGCA TTTGGTCTGA  
 27101 TTTTCCGGAC AGACCTCAAT AACTCTGTTT ACCAGAACAG GAGGTGAGCT  
 AAAAGGCCCTG TCTGGAGTTA TTGAGACAAA TGGTCTTGTC CTCCACTCGA  
 27151 TAGAAAACCC TTAGGGTATT AGGCCAAAGG CGCAGCTACT GTGGGGTTTA  
 ATCTTTTGGG AATCCATAA TCCGGTTTCC GCGTCGATGA CACCCCAAAT  
 27201 TGAACAATTC AAGCAACTCT ACGGGCTATT CTAATTCAGG TTTCTCTAGA  
 ACTTGTTAAG TTCGTTGAGA TGCCCGATAA GATTAAGTCC AAAGAGATCT  
 27251 ATCGGGGTTG GGGTTATTCT CTGTCTTGTG ATTCTCTTTA TTCTTATACT  
 TAGCCCCAAC CCCAATAAGA GACAGAACAC TAAGAGAAAT AAGAATATGA  
 27301 AACGCTTCTC TGCCTAAGGC TCGCCGCCCTG CTGTGTGCAC ATTGCAATT  
 TTGCGAAGAG ACGGATTCCG AGCGGCGGAC GACACACGTG TAAACGTAAA  
 27351 ATTGTCAGCT TTTTAAACGC TGGGGTCGCC ACCCAAGATG ATTAGGTACA  
 TAACAGTCGA AAAATTTGCG ACCCCAGCGG TGGGTTCTAC TAATCCATGT  
 27401 TAATCCTAGG TTTACTCACC CTTGCGTCAG CCCACGGTAC CACCCAAAAG  
 ATTAGGATCC AAATGAGTGG GAACGCAGTC GGGTGCCATG GTGGGTTTTC

Figure 27AC

27451 GTGGATTTTA AGGCCAGC CTGTAATGTT ACATTGCGAG CTGAAGGTA  
CACCTAAAAT TCCTCGGTCG GACATTACAA TGTAAGCGTC GACTTCGATT

27501 TGAGTGCACC ACTCTTATAA AATGCACCAC AGAACATGAA AAGCTGCTTA  
ACTCACGTGG TGAGAATATT TTACGTGGTG TCTTGACTT TTCGACGAAT

27551 TTCGCCACAA AAACAAAATT GGCAAGTATG CTGTTTATGC TATTTGGCAG  
AAGCGGTGTT TTTGTTTTAA CCGTTCATAC GACAAATACG ATAAACCGTC

27601 CCAGGTGACA CTACAGAGTA TAATGTTACA GTTTTCCAGG GTAAAGTCA  
GGTCCACTGT GATGTCTCAT ATTACAATGT CAAAAGGTCC CATTTTCAGT

27651 TAAACCTTTT ATGTATACTT TTCCATTTTA TGAAATGTGC GACATTACCA  
ATTTTGAAAA TACATATGAA AAGGTAAAT ACTTTACAG CTGTAATGGT

27701 TGTACATGAG CAAACAGTAT AAGTTGTGGC CCCACAAAA TTGTGTGGAA  
ACATGTACTC GTTGTCTATA TTCAACACCG GGGGTGTTTT AACACACCTT

27751 AACACTGGCA CTTTCTGCTG CACTGCTATG CTAATTACAG TGCTCGCTTT  
TTGTGACCGT GAAAGACGAC GTGACGATAC GATTAATGTC ACGAGCGAAA

27801 GGTCTGTACC CTACTCTATA TTAAATACAA AAGCAGACGC AGCTTTATTG  
CCAGACATGG GATGAGATAT AATTTATGTT TTCGTCTGCG TCGAAATAAC

27851 AGGAAAAGAA AATGCCTTAA TTTACTAAGT TACAAAGCTA ATGTCACCAC  
TCCTTTTCTT TTACGGAATT AATGATTCA ATGTTTCGAT TACAGTGGTG

27901 TAACTGCTTT ACTCGCTGCT TGCAAAACAA ATTCAAAAAG TTAGCATTAT  
ATTGACGAAA TGAGCGACGA ACGTTTTGTT TAAGTTTTTC AATCGTAATA

27951 AATTAGAATA GGATTTAAAC CCCCCGGTCA TTTCTGCTC AATACCATT  
TTAATCTTAT CCTAAATTG GGGGGCCAGT AAAGGACGAG TTATGGTAAG

28001 CCCTGAACAA TTGACTCTAT GTGGGATATG CTCCAGCGCT ACAACCTTGA  
GGGACTTGTT AACTGAGATA CACCCTATAC GAGGTGCGGA TGTGGAAC

28051 AGTCAGGCTT CTTGGATGTC AGCATCTGAC TTTGGCCAGC ACCTGTCCCG  
TCAGTCCGAA GGACCTACAG TCGTAGACTG AAACCGGTCG TGGACAGGGC

28101 CGGATTTGTT CCAGTCCAAC TACAGCGACC CACCCTAACA GAGATGACCA  
GCCTAAACAA GGTCAAGGTTG ATGTCGCTGG GTGGGATTGT CTCTACTGGT

28151 ACACAACCAA CGCGCCGCC GCTACCGGAC TTACATCTAC CACAAATACA  
TGTGTTGGTT GCGCCGGCGG CGATGGCCTG AATGTAGATG GTGTTTATGT

28201 CCCCAAGTTT CTGCCTTTGT CAATAACTGG GATAACTTGG GCATGTGGTG  
GGGGTTCAAA GACGGAAACA GTTATTGACC CTATTGAACC CGTACACCAC

28251 GTTCTCCATA GCGCTTATGT TTGTATGCCT TATTATTATG TGGCTCATCT  
CAAGAGGTAT CGCGAATACA AACATACGGA ATAATAATAC ACCGAGTAGA

28301 GCTGCCTAAA GCGCAAACGC GCCCGACCAC CCATCTATAG TCCCATCATT  
CGACGGATTT CCGGTTTCCG CCGGCTGGTG GGTAGATATC AGGGTAGTAA

28351 GTGCTACACC CAAACAATGA TGGAAATCCAT AGATTGGACG GACTGAAACA  
CACGATGTGG GTTTGTACT ACCTTAGGTA TCTAACCTGC CTGACTTTGT

Figure 27A D

28401 CATGTTCTTT TTTTACAG TATGATTAAA TGAGACATGA TTCCTCCTT  
GTACAAGAAA AGAGAATGTC ATACTAATTT ACTCTGTACT AAGGAGCTCA

28451 TTTTATATTA CTGACCCCTG TTGCGCTTTT TTGTGCGTGC TCCACATTGG  
AAAATATAAT GACTGGGAAC AACGCGAAA AACACGCACG AGGTGTAACC

28501 CTGCGGTTTC TCACATCGAA GTAGACTGCA TTCCAGCCTT CACAGTCTAT  
GACGCCAAAG AGTGTAGCTT CATCTGACGT AAGGTCGGAA GTGTCAGATA

28551 TTGCTTTACG GATTGTGCAC CCTCACGCTC ATCTGCAGCC TCATCACTGT  
AACGAAATGC CTAAACAGTG GGAGTGCAG TAGACGTCGG AGTAGTGACA

28601 GGTTCATCGCC TTTATCCAGT GCATTGACTG GGTCTGTGTG CGCTTTGCAT  
CCAGTAGCGG AAATAGGTCA CGTAACTGAC CCAGACACAC GCGAAACGTA

28651 ATCTCAGACA CCATCCCCAG TACAGGGACA GGACTATAGC TGAGCTTCTT  
TAGAGTCTGT GGTAGGGGTC ATGTCCTGT CCTGATATCG ACTCGAAGAA

28701 AGAATTCTTT AATTATGAAA TTTACTGTGA CTTTCTGTCT GATTATTTGC  
TCTTAAGAAA TTAATACTTT AAATGACACT GAAAAGACGA CTAATAAACG

28751 ACCCTATCTG CGTTTTGTTT CCCGACCTCC AAGCCTCAAA GACATATATC  
TGGGATAGAC GCAAAACAAG GGGCTGGAGG TTCGGAGTTT CTGTATATAG

28801 ATGCAGATTC ACTCGTATAT GGAATATTCC AAGTTGCTAC AATGAAAAAA  
TACGTCTAAG TGAGCATATA CCTTATAAGG TTCAACGATG TTACTTTTTT

28851 GCGATCTTTC CGAAGCCTGG TTATATGCAA TCATCTCTGT TATGGTGTTC  
CGCTAGAAAG GCTTCGGACC AATATACGTT AGTAGAGACA ATACCACAAG

28901 TECAGTACCA TCTTAGCCCT AGCTATATAT CCCTACCTTG ACATTGGCTG  
ACGTCATGGT AGAATCGGGA TCGATATATA GGGATGGAAC TGTAAACCGAC

28951 GAACGCAATA GATGCCATGA ACCACCCAAC TTTCCCCGCG CCCGCTATGC  
CTTCCGTTAT CTACGGTACT TGGTGGGTG AAAGGGGCGC GGGCGATACG

29001 TTCCACTGCA ACAAGTTGTT GCCGGCGGCT TTGTCCAGC CAATCAGCCT  
AAGGTGACGT TGTTCACAA CGGCCGCCGA AACAGGGTCG GTTAGTCGGA

29051 CGCCACCTT CCCCCACCC CACTGAAATC AGCTACTTTA ATCTAACAGG  
GCGGGTGGA GAGGCTGGG GTGACTTTAG TCGATGAAAT TAGATTGTCC

29101 AGGAGATGAC TGACACCCTA GATCTAGAAA TGGACGGAAT TATTACAGAG  
TCCTCTACTG ACTGTGGGAT CTAGATCTTT ACCTGCCCTA ATAATGTCTC

29151 CAGCGCCTGC TAGAAAGACG CAGGGCAGCG GCCGAGCAAC AGCGCATGAA  
GTGCGGGACG ATCTTTCTGC GTCCCGTCGC CGGCTCGTTG TCGCGTACTT

29201 TCAAGAGCTC CAAGACATGG TTAACCTGCA CCAGTGCAA AGGGGTATCT  
AGTTCTCGAG GTTCTGTACC AATTGAACGT GGTACGTTT TCCCCATAGA

29251 TTTGTCTCGT AAAGCAGGCC AAAGTCACCT ACGACAGTAA TACCACCGGA  
AAACAGAGCA TTTCGTCCGG TTTCAGTGA TGCTGTCAAT ATGGTGGCCT

29301 CACCGCCTTA GCTACAAGTT GCCAACCAAG CGTCAGAAAT TGGTGGTCAT  
GTGGCGGAAT CGATGTTCAA CGTTGGTTC GCAGTCTTTA ACCACCAGTA

Figure 27 A E

29351 GGTGGGAGAA A~~CC~~ATTTC CCATAACTCA GCACTCGGTA GAAACC~~CG~~  
CCACCCTCTT TTCGGGTAAT GGTATTGAGT CGTGAGCCAT CTTTGGCTTC

29401 GCTGCATTCA CTCACCTTGT CAAGGACCTG AGGATCTCTG CACCCCTTATT  
CGACGTAAGT GAGTGGAAACA GTTCCTGGAC TCCTAGAGAC GTGGGAATAA

29451 AAGACCCTGT GCGGTCTCAA AGATCTTATT CCCTTTAACT AATAAAAAAA  
TTCTGGGACA CGCCAGAGTT TCTAGAATAA GGGAAATTGA TTATTTTTTT

29501 AATAATAAAG CATCACTTAC TTAAAATCAG TTAGCAAATT TCTGTCCAGT  
TTATTATTTC GTAGTGAATG AATTTTAGTC AATCGTTTAA AGACAGGTCA

29551 TTATTCAGCA GCACCTCCTT GCCCTCCTCC CAGCTCTGGT ATTGCAGCTT  
AATAAGTCGT CGTGGAGGAA CGGGAGGAGG GTCGAGACCA TAACGTCGAA

29601 CCTCCTGGCT GCAAACTTTC TCCACAATCT AAATGGAATG TCAGTTTCCT  
GGAGGACCGA CGTTTGAAAG AGGTGTTAGA TTTACCTTAC AGTCAAAGGA

29651 CCTGTTCTCG TCCATCCGCA CCCACTATCT TCATGTTGTT GCAGATGAAG  
GGACAAGGAC AGGTAGGCGT GGGTGATAGA AGTACAACAA CGTCTACTTC

29701 CGCGCAAGAC CGTCTGAAGA TACCTTCAAC CCCGTGTATC CATATGACAC  
GCGCGTTCTG GCAGACTTCT ATGGAAGTTG GGGCACATAG GTATACTGTG

29751 GGAAACCGGT CCTCCAACG TGCCTTTTCT TACTCTCCC TTTGTATCCC  
CCTTTGGCCA GGAGGTTGAC ACGGAAAAGA ATGAGGAGGG AACATAGGG

29801 CCAATGGGTT TCAAGAGAGT CCCCCGCGG TACTCTCTTT GCGCCTATCC  
GGTTACCCAA AGTTCTCTCA GGGGGACCC ATGAGAGAAA CGCGGATAGG

29851 GAACCTCTAG TTACCTCCAA TGGCATGCTT GCGCTCAAAA TGGGCAACGG  
CTTGGAGATC AATGGAGGTT ACCGTACGAA CGCGAGTTTT ACCCGTTGCC

29901 CCTCTCTCTG GACGAGGCCG GCAACCTTAC CTCCCCAAAT GTAACCACTG  
GGAGAGAGAC CTGCTCCGGC CGTTGGAATG GAGGGTTTTA CATTGGTGAC

29951 TGAGCCCACC TCTCAAAAAA ACCAAGTCAA ACATAAACCT GGAAATATCT  
ACTCGGGTGG AGAGTTTTTT TGGTTCAGTT TGTATTTGGA CCTTTATAGA

30001 GCACCCCTCA CAGTTACCTC AGAAGCCCTA ACTGTGGCTG CCGCCGCACC  
CGTGGGGAGT GTCAATGGAG TCTTCGGGAT TGACACCGAC GCGGGCGTGG

30051 TCTAATGGTC GCGGGCAACA CACTCACCAT GCAATCACAG GCCCCGCTAA  
AGATTACCAG CGCCCGTTGT GTGAGTGGTA CGTTAGTGTC CGGGGCGATT

30101 CCGTGACCGA CTCCAAACTT AGCATTGCCA CCCAAGGACC CCTCACAGTG  
GGCACGTGCT GAGGTTTGAA TCGTAACGGT GGGTTCCTGG GGAGTGTCAC

30151 TCAGAAGGAA AGCTAGCCCT GCAAACATCA GGGCCCCCTCA CCACCACCGA  
AGTCTTCCTT TCGATCGGGA CGTTGTAGT CCGGGGGAGT GGTGGTGGCT

30201 TAGCAGTACC CTTACTATCA CTGCCTCACC CCCTCTAACT ACTGCCACTG  
ATCGTCATGG GAATGATAGT GACGGAGTGG GGGAGATTGA TGACGGTGAC

30251 GTAGCTTGGG CATTGACTTG AAAGAGCCCA TTTATACACA AAATGGAAAA  
CATCGAACCC GTAACGAAC TTTCTCGGGT AAATATGTGT TTTACCTTTT

Figure 27 AF

30301 CTAGGACTAA AGCGGGGC TCCTTTGCAT GTAACAGACG ACCTAAAC  
GATCCTGATT TCGGCCCCG AGGAAACGTA CATTGTCTGC TGGATTTCG

30351 TTTGACCGTA GCAACTGGTC CAGGTGTGAC TATTAATAAT ACTTCCTTGC  
AAACTGGCAT CGTTGACCAG GTCCACACTG ATAATTATTA TGAAGGAACG

30401 AAATAAAGT TACTGGAGCC TTGGGTTTTG ATTCACAAGG CAATATGCAA  
TTTGATTTCA ATGACCTCGG AACCCAAAAC TAAGTGTTC GTTATACGTT

30451 CTTAATGTAG CAGGAGGACT AAGGATTGAT TCTCAAAACA GACGCCTTAT  
GAATTACATC GTCCTCCTGA TTCCTAACTA AGAGTTTTGT CTGCGGAATA

30501 ACTTGATGTT AGTTATCCGT TTGATGCTCA AAACCAACTA AATCTAAGAC  
TGAATAACAA TCAATAGGCA AACTACGAGT TTTGGTTGAT TTAGATTCTG

30551 TAGGACAGGG CCCTCTTTTT ATAACTCAG CCCACAACCT GGATATTAAC  
ATCCTGTCCC GGGAGAAAAA TATTTGAGTC GGGTGTGAA CCTATAATTG

30601 TACAACAAAG GCCTTTACTT GTTTACAGCT TCAAACAATT CCAAAAAGCT  
ATGTTGTTTC CGGAAATGAA CAAATGTGCA AGTTTGTAA GGTTTTTCGA

30651 TGAGGTTAAC CTAAGCACTG CCAAGGGGTT GATGTTTGAC GCTACAGCCA  
ACTCCAATTG GATTCGTGAC GGTCCCCAA CTACAACTG CGATGTCGGT

30701 TAGCCATTAA TGCAGGAGAT GGGCTTGAAT TTGGTTCACC TAATGCACCA  
ATCGGTAATT ACGTCCTCTA CCCGAACCTA AACCAAGTGG ATTACGTGGT

30751 AACACAAATC CCCTCAAAAC AAAAATTGGC CATGGCCTAG AATTTGATTC  
TTGTGTTTAG GGGAGTTTTG TTTTAAACCG GTACCGGATC TTAAACTAAG

30801 AAACAAGGCT ATGGTTCCTA AACTAGGAAC TGGCCTTAGT TTTGACAGCA  
TTGTTCCTGA TACCAAGGAT TTGATCCTTG ACCGGAATCA AAAGTGTGCT

30851 CAGGTGCCAT TACAGTAGGA AACAAAAATA ATGATAAGCT AACTTTGTGG  
GTCCACGGTA ATGTCATCCT TTGTTTTAT TACTATTGCA TTGAAACACC

30901 ACCACACCAG CTCATCTCC TAACTGTAGA CTAAATGCAG AGAAAGATGC  
TGGTGTGGTC GAGGTAGAGG ATTGACACTT GATTACGTC TCTTTCTACG

30951 TAACTCACT TTGGTCTTAA CAAATGTGG CAGTCAAATA CTTGCTACAG  
ATTTGAGTGA AACCAGAATT GTTTTACACC GTCAGTTTAT GAACGATGTC

31001 TTTCAGTTTT GGCTGTAAA GGCAGTTTGG CTCCAATATC TGGAACAGTT  
AAAGTCAAAA CCGACAATT CCGTCAAACC GAGGTTATAG ACCTTGTCAA

31051 CAAAGTGCTC ATCTTATTAT AAGATTTGAC GAAATGGAG TGCTACTAAA  
GTTTCACGAG TAGAATAATA TTCTAACTG CTTTACCTC ACGATGATTT

31101 CAATTCCTTC CTGGACCCAG AATATTGGAA CTTTAGAAAT GGAGATCTTA  
GTTAAGGAAG GACCTGGGTC TTATAACCTT GAAATCTTTA CCTCTAGAAT

31151 CTGAAGGCAC AGCCTATACA AACGCTGTTG GATTTATGCC TAACCTATCA  
GACTTCCGTG TCGGATATGT TTGCGACAAC CTAAATACGG ATTGGATAGT

31201 GCTTATCCAA AATCTCACGG TAAACTGCC AAAAGTAACA TTGTCAGTCA  
CGAATAGGTT TTAGAGTGCC ATTTGACGG TTTTCATTGT AACAGTCAGT

Figure 27 AG

31251 AGTTTACTTA AAGGAGACA AACTAAACC TGTAACACTA ACCATTAC  
 TCAATGAAT TTGCCTCTGT TTTGATTGG ACATTGTGAT TGGTAATGTG  
 31301 TAAACGGTAC ACAGGAAACA GGAGACACAA CTCCAAGTGC ATACTCTATG  
 ATTTGCCATG TGTCCTTTGT CCTCTGTGTT GAGGTTACAG TATGAGATAC  
 31351 TCATTTTCAT GGGACTGGTC TGGCCACAAC TACATTAATG AAATATTTGC  
 AGTAAAAGTA CCCTGACCAG ACCGGTGTG ATGTAATTAC TTTATAAACG  
 31401 CACATCCTCT TACACTTTTT CATACTTGC CCAAGAATAA AGAATCGTTT  
 GTGTAGGAGA ATGTGAAAAA GTATGTAACG GGTTCCTATT TCTTAGCAAA  
 31451 GTGTTATGTT TCAACGTGTT TATTTTTCAA TTGCAGAAAA TTTCAAGTCA  
 CACAATACAA AGTTGCACAA ATAAAAAGTT AACGTCCTTT AAAGTTCAGT  
 31501 TTTTTCATTC AGTAGTATAG CCCCACCACC ACATAGCTTA TACAGATCAC  
 AAAAGTAAG TCATCATATC GGGGTGGTGG TGTATCGAAT ATGTCTAGTG  
 31551 CGTACCTTAA TCAAATCAC AGAACCTAG TATTCAACCT GCCACCTCCC  
 GCATGGAATT AGTTTGAGTG TCTTGGGATC ATAAGTTGGA CGGTGGAGGG  
 31601 TCCCAACACA CAGAGTACAC AGTCCTTTCT CCCCAGGCTGG CCTTAAAAAG  
 AGGTTGTGT GTCTCATGTG TCAGGAAAGA GGGGCCGACC GGAATTTTTC  
 31651 CATCATATCA TGGGTAACAG ACATATCTTT AGGTGTTATA TTCCACACGG  
 GTAGTATAGT ACCCATTGTC TGTATAAGAA TCCACAATAT AAGGTGTGCC  
 31701 TTTCTGTGCG AGCCAAACGC TCATCAGTGA TATTAATAAA CTCCCCGGGC  
 AAAGGACAGC TCGGTTTGCG AGTAGTCACT ATAATTATTT GAGGGGCCCG  
 31751 AGCTCACITA AGTTCATGTC GCTGTCCAGC TGCTGAGCCA CAGGCTGCTG  
 TCGAGTGAAT TCAAGTACAG CGACAGGTG ACGACTCGGT GTCCGACGAC  
 31801 TCCAACTTGC GGTGCTTAA CGGGCGGCGA AGGAGAAGTC CACGCCTACA  
 AGGTTGAACG CCAACGAATT GCCCGCCGCT TCCTCTTCAG GTGCGGATGT  
 31851 TGGGGGTAGA GTCATAATCG TGCATCAGGA TAGGGCGGTG GTGCTGCAGC  
 ACCCCCATCT CAGTATTAGC ACGTAGTCTT ATCCCGCCAC CACGACGTG  
 31901 AGCGCGCGAA TAACTGCTG CCGCCGCCGC TCCGTCTGCG AGGAATACAA  
 TCGCGCGCTT ATTTGACGAC GCGCGCGCG AGGCAGGACG TCCTTATGTT  
 31951 CATGGCAGTG GTCTCCTCAG CGATGATTG CACCGCCCGC AGCATAAGGC  
 GTACCGTCAC CAGAGGAGTC GCTACTAAGC GTGGCGGGCG TCGTATTCCG  
 32001 GCCTTGTCCT CCGGCGACAG CAGCGCACC TGATCTCACT TAAATCAGCA  
 CGGAACAGGA GGCCCGTGTG GTCGCGTGGG ACTAGAGTGA ATTTAGTCGT  
 32051 CAGTAACTGC AGCACAGCAC CACAATATTG TTCAAAATCC CACAGTGCAA  
 GTCATTGACG TCGTGTCTG GTGTTATAAC AAGTTTTAGG GTGTCACGTT  
 32101 GCGCTGTAT CCAAAGCTCA TGGCGGGGAC CACAGAACCC ACGTGGCCAT  
 CCGCGACATA GGTTCGAGT ACCGCCCTG GTGTCTTGGG TGCACCGGTA  
 32151 CATACCACAA GCGCAGGTAG ATTAAGTGGC GACCCCTCAT AAACACGCTG  
 GTATGGTGT CCGCTCCATC TAATTACCG CTGGGGAGTA TTTGTGCGAC

Figure 27AH

32201 GACATAAACA TCTCTTT TGGCATGTTG TAATTCACCA CCTCCC  
 CTGTATTTGT AATGGAGAAA ACCGTACAAC ATTAAGTGGT GGAGGGCCAT  
 32251 CCATATAAAC CTCTGATTAA ACATGGCGCC ATCCACCACC ATCCTAAACC  
 GGTATATTTG GAGACTAATT TGTACC GCGG TAGGTGGTGG TAGGATTTGG  
 32301 AGCTGGCCAA AACCTGCCCC CCGGCTATAC ACTGCAGGGA ACCGGGACTG  
 TCGACCGGTT TTGGACGGGC GGCCGATATG TGACGTCCCT TGGCCCTGAC  
 32351 GAACAATGAC AGTGGAGAGC CCAGGACTCG TAACCATGGA TCATCATGCT  
 CTTGTTACTG TCACCTCTCG GGTCTGAGC ATTGGTACCT AGTAGTACGA  
 32401 CGTCATGATA TCAATGTTGG CACAACACAG GCACACGTGC ATACACTTCC  
 GCAGTACTAT AGTTACAACC GTGTTGTGTC CGTGTGCACG TATGTGAAGG  
 32451 TCAGGATTAC AAGCTCCTCC CGCGTTAGAA CCATATCCCA GGAACAAC  
 AGTCCTAATG TTCGAGGAGG GCGCAATCTT GGTATAGGGT CCCTTGTTGG  
 32501 CATTCCTGAA TCAGCGTAAA TCCCACACTG CAGGGAAGAC CTCGCACGTA  
 GTAAGGACTT AGTCGCATTT AGGGTGTGAC GTCCCTCTCG GAGCGTGCAT  
 32551 ACTCACGTTG TGCATTGTCA AAGTGTTACA TTCGGGCAGC AGCGGATGAT  
 TGAGTGCAAC ACGTAACAGT TTCACAATGT AAGCCCCTCG TCGCCTACTA  
 32601 CCTCCAGTAT GGTAGCGCGG GTTTCGTGCT CAAAAGGAGG TAGACGATCC  
 GGAGGTCATA CCATCGCGCC CAAAGACAGA GTTTCTCTCC ATCTGCTAGG  
 32651 CTACTGTACG GAGTGCGCCG AGACAACCGA GATCGTGTG TCGTAGTGT  
 GATGACATGC CTCACGCGGC TCTGTTGCT CTAGCACAA CAGCATCACA  
 32701 CATGCCAAAT GGAACGCCGG ACGTAGTCAT ATTTCTGAA GCAAAACCAG  
 GTACGGTTTA CCTTGCGGCC TGCATCAGTA TAAAGGACTT CGTTTGGTC  
 32751 GTCGGGGCGT GACAAACAGA TCTGCGTCT CGGTCTCGCC GCTTAGATCG  
 CACGCCCCGA CTGTTGTCT AGACGCAAG GCCAGAGCGG CGAATCTAGC  
 32801 CTCTGTGTAG TAGTTGTAGT ATATCCAATC TCTCAAAGCA TCCAGGCGCC  
 GAGACACATC ATCAACATCA TATAGGTGAG AGAGTTTCGT AGGTCCGCGG  
 32851 CCCTGGCTTC GGGTCTATG TAAACTCCTT CATGCGCCGC TCCCTGATA  
 GGGACCGAAG CCCAAGATAC ATTTGAGGAA GTACGCGCGG ACGGGACTAT  
 32901 ACATCCACCA CCGCAGAATA AGCCACACCC AGCCAACCTA CACATTTCGT  
 TGTAGGTGGT GGCCTCTTAT TCGGTGTGGG TCGGTGGAT GTGTAAGCAA  
 32951 CTGCGAGTCA CACACGGGAG GAGCGGGAAG AGCTGGAAGA ACCATGTTTT  
 GACGCTCAGT GTGTGCCCTC CTCGCCCTTC TCGACCTTCT TGGTACAAAA  
 33001 TTTTTTTATT CAAAAGATT ATCCAAAACC TCAAAATGAA GATCTATTAA  
 AAAAAATAA GGTTTTCTAA TAGGTTTGG AGTTTACTT CTAGATAATT  
 33051 GTGAACGCGC TCCCTCCGG TGGCGTGGTC AACTCTACA GCCAAAGAAC  
 CACTTGC GCG AGGGGAGGCC ACCGCACCAG TTTGAGATGT CGGTTTCTTG  
 33101 AGATAATGGC ATTGTGAAGA TGTGACAAA TGGCTTCAA AAGGCAAACG  
 TCTATTACCG TAAACATTCT ACAACGTGTT ACCGAAGGTT TTCCGTTTGC

Figure 27 AI

33151 GCCCTCACGT GTGGAC GTAAAGGCTA AACCCCTTCAG GGTGAAATTC  
 CGGGAGTGCA GGTTCACCTG CATTTCGGAT TTGGGAAGTC CCACTTAAAG  
 33201 CTCTATAAAC ATTCCAGCAC CTTCAACCAT GCCCAAATAA TTCTCATCTC  
 GAGATATTTG TAAGGTCGTG GAAGTTGGTA CGGGTTTATT AAGAGTAGAG  
 33251 GCCACCTTCT CAATATATCT CTAAGCAAAT CCCGAATATT AAGTCCGGCC  
 CGGTGGAAGA GTTATATAGA GATTCTGTTA GGGCTTATAA TTCAGGCCGG  
 33301 ATTGTAAAAA TCTGCTCCAG AGCGCCCTCC ACCTTCAGCC TCAAGCAGCG  
 TAACATTTTT AGACGAGGTC TCGCGGGAGG TGGAAAGTCGG AGTTCGTCGC  
 33351 AATCATGATT GCAAAAATTC AGGTTCCTCA CAGACCTGTA TAAGATTCAA  
 TTAGTACTAA CGTTTTTAAG TCCAAGGAGT GTCTGGACAT ATTCTAAGTT  
 33401 AAGCGGAACA TTAACAAAAA TACCGCGATC CCGTAGGTCC CTTGCGAGGG  
 TTCGCTTGT AATGTTTTT ATGGCGCTAG GGCATCCAGG GAAGCGTCCC  
 33451 CCAGCTGAAC ATAATCGTGC AGGTCTGCAC GGACCAGCGC GGCCACTTCC  
 GGTGCACTTG TATTAGCACG TCCAGACGTG CCTGGTCGCG CCGGTGAAGG  
 33501 CCGCCAGGAA CCATGACAAA AGAACCACA CTGATTATGA CACGCATACT  
 GGGGTCCTT GGTACTGTTT TCTTGGGTGT GACTAATACT GTGCGTATGA  
 33551 CGGAGCTATG CTAACCAGCG TAGCCCCGAT GTAAGCTTGT TGCATGGGCG  
 GCCTCGATAC GATTGGTCGC ATCGGGGCTA CATTGGAACA ACGTACCCGC  
 33601 GCGATATAAA ATGCAAGGTG CTGCTCAAAA AATCAGGCAA ACCCTCGCGC  
 CGCTATATTT TACGTTCCAC GACGAGTTTT TTAGTCCGTT TCGGAGCGCG  
 33651 AAAAAAGAAA GCACATCGTA GTCATGCTCA TGCAGATAAA GGCAGGTAAG  
 TTTTTCTTT CGTGTAGCAT CAGTACGAGT ACGTCTATTT CCGTCCATT  
 33701 CTCCGGAACC ACCACAGAAA AAGACACCAT TTTCTCTCA AACATGTCTG  
 GAGGCCTTGG TGGTGTCTTT TTCTGTGTA AAAAGAGAGT TTGTACAGAC  
 33751 CGGGTTTCTG CATAAACACA AAATAAATA ACAAAAAAAC ATTTAAACAT  
 GCCCAAAGAC GTATTTGTGT TTTATTTTAT TGTTTTTTTG TAAATTTGTA  
 33801 TAGAAGCCTG TCTTACAACA GGA AAAACA CCCTTATAAG CATAAGACGG  
 ATCTTCGGAC AGAATGTTGT CCTTTTGTG GGAATATTC GTATTCTGCC  
 33851 ACTACGGCCA TGCCGGCGTG ACCGTAAAAA AACTGGTCAC CGTGATTAAA  
 TGATGCCGCT ACGGCCGCAC TGGCATTTTT TTGACCAGTG GCACTAATTT  
 33901 AAGCACCACC GACAGCTCCT CGGTCAATGC CGGAGTCATA ATGTAAGACT  
 TTCGTGGTGG CTGTCGAGGA GCCAGTACAG GCCTCAGTAT TACATTCTGA  
 33951 CGGTAAACAC ATCAGGTTGA TTCACATCGG TCAGTGCTAA AAAGCGACCG  
 GCCATTTGTG TAGTCCAAC TAAAGTAGCC AGTCACGATT TTTGCTGGC  
 34001 AAATAGCCCG GGGGAATACA TACCCGACAG CGTAGAGACA ACATTACAGC  
 TTTATCGGGC CCCCTTATGT ATGGGCGTCC GCATCTCTGT TGTAAATGTCG  
 34051 CCCCATAGGA GGTATAACAA AATTAATAGG AGAGAAAAAC ACATAAACAC  
 GGGGTATCCT CCATATTGTT TTAATTATCC TCTCTTTTGT TGTATTTGTG

Figure 27A J

34101 CTGAAAAACC CCGTTGCCTA GGCAAAATAG CACCCTCCCG ~~CTGCACTA~~  
 GACTTTTGGG ~~GACGAT~~ CCGTTTATC GTGGGAGGGC GAGGTC ~~CT~~  
 34151 ACATACAGCG CTTCCACAGC GGCAGCCATA ACAGTCAGCC TTACCAGTAA  
 TGTATGTCGC GAAGGTGTCG CCGTCGGTAT TGTCACTCGG AATGGTCATT  
 34201 AAAAGAAAAC CTATTAAAA AACACCACTC GACACGGCAC CAGCTCAATC  
 TTTCTTTTG GATAATTTT TTGTGGTGAG CTGTGCCGTG GTCGAGTTAG  
 34251 AGTCACAGTG TAAAAAAGGG CCAAGTGCAG AGCGAGTATA TATAGGACTA  
 TCAGTGTACG ATTTTTCCTC GGTTCACGTC TCGCTCATAT ATATCCTGAT  
 34301 AAAAATGACG TAACGGTTAA AGTCCACAAA AAACCCACAG AAAACCGCAC  
 TTTTACTGCG ATTGCCAATT TCAGGTGTTT TTTGTGGGTC TTTTGGCGTG  
 34351 GCGAACCTAC GCCCAGAAAC GAAAGCCAAA AAACCCACAA CTTCTCTAAA  
 CGCTTGGATG CGGGTCTTTG CTTTCGGTTT TTTGGGTGTT GAAGGAGTTT  
 34401 TCGTCACTTC CGTTTTCCTA CGTTACGTCA CTTCCCATTT TAAGAAAAC  
 AGCAGTGAAG GCAAAAGGGT GCAATGCAGT GAAGGGTAAA ATTCTTTTGA  
 34451 ACAATTCCCA ACACATACAA GTTACTCCGC CCTAAAACCT ACCTCACCCG  
 TGTAAAGGGT TGTGTATGTT CAATGAGGCG GGATTTTGA TGCAGTGGGC  
 34501 CCCCCTTCCC ACGCCCCGCG CCACGTCACA AACTCCACCC CCTCATTATC  
 GGGGCAAGGG TCGGGGGCGC GGTGCAGTGT TTGAGGTGGG GGAGTAATAG  
  

PacI  
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 34551 ATATTGGCTT CAATCCAAAA TAAGGTATAT TATTGATGAT GTTAATTAAG  
 TATAACCGAA GTTAGGTTTT ATTCCATATA ATAACCTACTA CAATTAATTC  
 34601 AATTTCGGATC TGCGACGCGA GGCTGGATGG CCTTCCCAT TATGATTCTT  
 TTAAGCCTAG ACGCTGCGCT CCGACCTACC GGAAGGGGTA ATACTAAGAA  
 34651 CTCGCTTCCG GCGGCATCGG GATGCCCCGCG TTGCAGGCCA TGCTGTCCAG  
 GAGCGAAGGC CGCCGTAGCC CTACGGGCGC AACGTCCGGT ACGACAGGTC  
 34701 GCAGGTAGAT GACGACCATC AGGGACAGCT TCAAGGCCAG CAAAAGGCCA  
 CGTCCATCTA CTGCTGGTAG TCCCTGTCTGA AGTTCCGGTC GTTTTCCGGT  
 34751 GGAACCGTAA AAAGGCCGCG TTGCTGGCGT TTTTCCATAG GCTCCGCCCC  
 CCTTGGCATT TTTCCGGCGC AACGACCGCA AAAAGGTATC CGAGGCGGGG  
 34801 CCTGACGAGC ATCACAACAAA TCGACGCTCA AGTCAGAGGT GCGGAAACCC  
 GGACTGCTCG TAGTGTTTTT AGCTGCGAGT TCAGTCTCCA CCGCTTTGGG  
 34851 GACAGGACTA TAAAGATACC AGGCGTTTCC CCCTGGAAGC TCCCTCGTGC  
 CTGTCTGAT ATTTCTATGG TCCGCAAAGG GGGACCTTCG ACGGAGCACG  
 34901 GCTCTCCTGT TCCGACCCTG CCGCTTACCG GATACCTGTC CGCCTTTCTC  
 CGAGAGGACA AGGCTGGGAC GCGGAATGGC CTATGGACAG GCGGAAAGAG  
 34951 CCTTCGGGAA GCGTGGCGCT TTCTCATAGC TCACGCTGTA GGTATCTCAG  
 GGAAGCCCTT CGCACCAGCA AAGAGTATCG AGTGCGACAT CCATAGAGTC  
 35001 TTCGGTGTAG GTCGTTGCT CCAAGCTGGG CTGTGTGCAC GAACCCCCCG  
 AAGCCACATC CAGCAAGCGA GGTTCGACCC GACACACGTG CTTGGGGGGC

Figure 27 AK

35051 TTCAGCCCGA CCGCTGCGCC TTATCCGGTA ACTATCGTCT TGAGTCCAAAC  
AAGTCGGGCT GCGGACGCGG AATAGGCCAT TGATAGCAGA ACTCAGGTTG

35101 CCGGTAAGAC ACGACTTATC GCCACTGGCA GCAGCCACTG GTAACAGGAT  
GGCCATTCTG TGCTGAATAG CGGTGACCGT CGTCGGTGAC CATTGTCTTA

35151 TAGCAGAGCG AGGTATGTAG GCGGTGCTAC AGAGTTCTTG AAGTGGTGGC  
ATCGTCTCGC TCCATACATC CGCCACGATG TCTCAAGAAC TTCACCACCG

35201 CTAACTACGG CTACACTAGA AGGACAGTAT TTGGTATCTG CGCTCTGCTG  
GATTGATGCC GATGTGATCT TCCTGTCATA AACCATAGAC GCGAGACGAC

35251 AAGCCAGTTA CCTTCGGAAA AAGAGTTGGT AGCTCTTGAT CCGGCAAACA  
TTCGGTCAAT GGAAGCCTTT TTCTCAACCA TCGAGAACTA GGCCGTTTGT

35301 AACCACCCTG GGTAGCGGTG GTTTTTTTGT TTGCAAGCAG CAGATTACGC  
TTGGTGCGCA CCATCGCCAC CAAAAAACA AACGTTCTGTC GTCTAATGCG

35351 GCAGAAAAAA AGGATCTCAA GAAGATCCTT TGATCTTTTC TACGGGGTCT  
CGTCTTTTTT TCCTAGAGTT CTCTAGGAA ACTAGAAAAG ATGCCCCAGA

35401 GACGCTCAGT GGAACGAAAA CTCACGTAA GGGATTTTGG TCATGAGATT  
CTGCGAGTCA CCTTGCTTTT GAGTGCAATT CCCTAAAACC AGTACTCTAA

35451 ATCAAAAAGG ATCTTCACCT AGATCCTTTT AAATCAATCT AAAGTATATA  
TAGTTTTTCC TAGAAGTGA TCTAGGAAAA TTTAGTTAGA TTTCATATAT

35501 TGAGTAACT TGGTCTGACA GTTACCAATG CTTAATCAGT GAGGCACCTA  
ACTCATTTGA ACCAGACTGT CAATGGTTAC GAATTAGTCA CTCCGTGGAT

35551 TCTCAGCGAT CTGTCTATTT CGTTCATCCA TAGTTGCCTG ACTCCCCGTC  
AGAGTCGCTA GACAGATAAA GCAAGTAGGT ATCAACGGAC TGAGGGGCAG

35601 GTGTAGATAA CTACGATACG GGAGGGCTTA CCATCTGGCC CCAGTGCTGC  
CACATCTATT GATGCTATGC CCTCCCGAAT GGTAGACCGG GGTCACGACG

35651 AATGATACCG CGAGACCCAC GCTCACCGGC TCCAGATTTA TCAGCAATAA  
TTACTATGGC GCTCTGGGTG CGAGTGCCCG AGGTCTAAAT AGTCGTTATT

35701 ACCAGCCAGC CGGAAGGGCC GAGCGCAGAA GTGGTCTTGC AACTTTATCC  
TGGTCGGTCG GCCTTCCCGG CTCGCGTCTT CACCAGGACG TTGAAATAGG

35751 GCCTCCATCC AGTCTATTAA TTGTGCGCGG GAAGCTAGAG TAAGTAGTTC  
CGGAGGTAGG TCAGATAATT AACAACGGCC CTTCGATCTC ATTCATCAAG

35801 GCCAGTTAAT AGTTTGCGCA ACGTTGTTGC CATTGCTACA GGCATCGTGG  
CGGTCAATTA TCAAACGCGT TGCAACAACG GTAACGATGT CCGTAGCACC

35851 TGTCACGCTC GTCGTTTGGT ATGGCTTCAT TCAGCTCCGG TTCCCAACGA  
ACAGTGCGAG CAGCAAACCA TACCGAAGTA AGTCGAGGCC AAGGGTTGCT

35901 TCAAGGCGAG TTACATGATC CCCCATGTTG TGCAAAAAG CGGTTAGCTC  
AGTTCCGCTC AATGTACTAG GGGGTACAAC ACGTTTTTTC GCCAATCGAG

35951 CTTGGGTCTT CCGATCGTTG TCAGAAGTAA GTTGGCCGCA GTGTTATCAC  
GAAGCCAGGA GGCTAGCAAC AGTCTTCATT CAACCGGCGT CACAATAGTG

Figure 2 AL

36001 TCATGGTTAT ~~US~~AGCACTG CATAATTCTC TTACTGTCAT GCCATC~~TA~~  
AGTACCAATA CCGTCGTGAC GTATTAAGAG AATGACAGTA CGGTAGGCAT

36051 AGATGCTTTT CTGTGACTGG TGAGTACTCA ACCAAGTCAT TCTGAGAATA  
TCTACGAAAA GACACTGACC ACTCATGAGT TGGTTCAGTA AGACTCTTAT

36101 GTGTATGCGG CGACCGAGTT GCTCTTGCCC GCGGTCAACA CGGGATAATA  
CACATACGCC GCTGGCTCAA CGAGAACGGG CCGCAGTTGT GCCCTATTAT

36151 CCGCGCCACA TAGCAGAACT TTAAGAGTGC TCATCATTGG AAAACGTTCT  
GGCGCGGTGT ATCGTCTTGA AATTTTCACG AGTAGTAACC TTTTGCAAGA

36201 TCGGGGCGAA AACTCTCAAG GATCTTACCG CTGTTGAGAT CCAGTTCGAT  
AGCCCCGCTT TTGAGAGTTC CTAGAATGGC GACAACTCTA GGTCAAGCTA

36251 GTAACCCACT CGTGACCCCA ACTGATCTTC AGCATCTTTT ACTTTCACCA  
CATTGGGTGA GCACGTGGGT TGACTAGAAG TCGTAGAAAA TGAAAGTGGT

36301 GCGTTTCTGG GTGAGCAAAA ACAGGAAGGC AAAATGCCGC AAAAAAGGGA  
CGCAAAGACC CACTCGTTTT TGTCCTTCCG TTTTACGGCG TTTTTTCCCT

36351 ATAAGGGCGA CACGGAAATG TTGAATACTC ATACTCTTCC TTTTCAATA  
TATTCCCGCT GTGCCTTTAC AACTTATGAG TATGAGAAGG AAAAAGTTAT

36401 TTATTGAAGC ATTTATCAGG GTTATTGTCT CATGAGCGGA TACATATTTG  
AATAACTTCG TAAATAGTCC CAATAACAGA GTACTCGCCT ATGTATAAAC

36451 AATGTATTTA GAAAAATAAA CAAATAGGGG TTCCGCGCAC ATTTCCCCGA  
TTACATAAAT CTTTTTATTT GTTTATCCCC AAGGCGCGTG TAAAGGGGCT

36501 AAAGTGCCAC CTGACGTCTA AGAAACCATT ATTATCATGA CATTACCTA  
TTTCACGGTG GACTGCAGAT TCITTGGTAA TAATAGTACT GTAATTGGAT

36551 TAAAAATAGG CGTATCACGA GGCCCTTTTCG TCTTCAAGAA TTGGATCCGA  
ATTTTTATCC GCATAGTGCT CCGGGAAGC AGAAGTTCTT AACCTAGGCT

PacI

36601 ATTCTTAATT TCTTAATTAA (SEQ ID NO:34)  
TAAGAATTAA AGAATTAATT (SEQ ID NO:35)

*Figure 27AM*

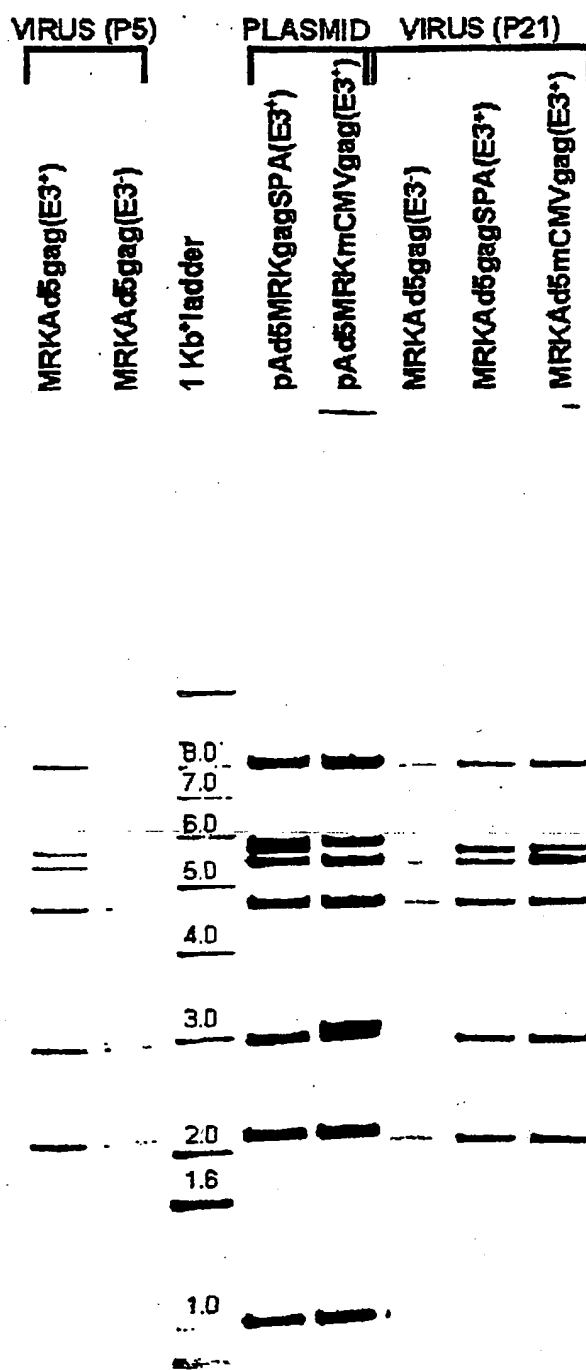


FIGURE 28

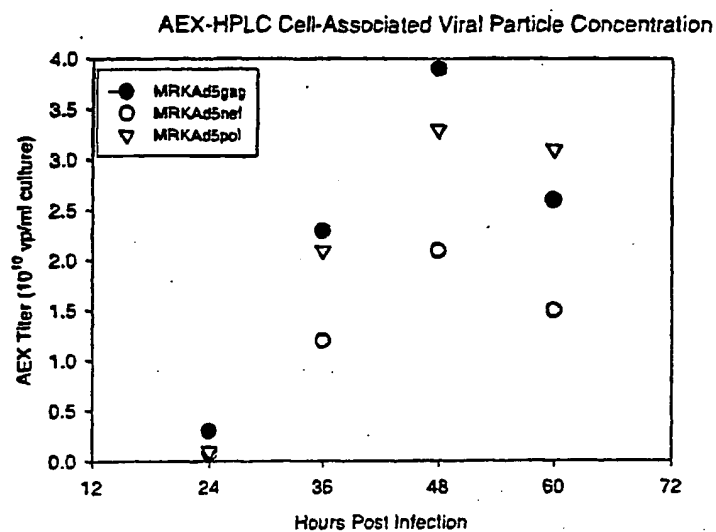


FIGURE 29A

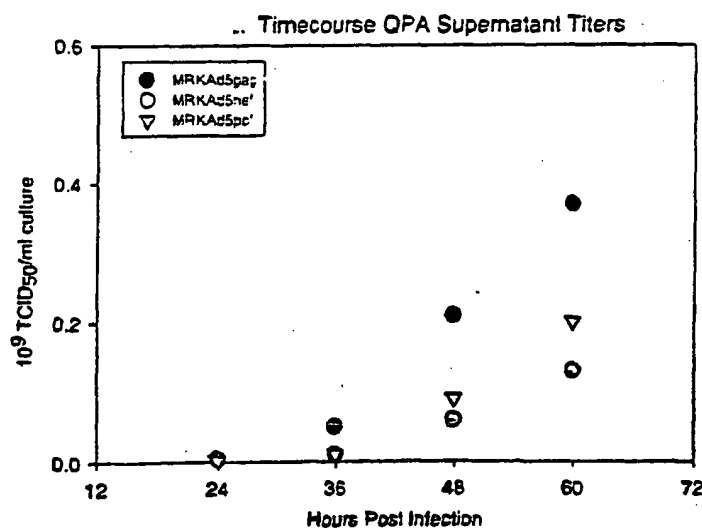


FIGURE 29B

atg gat gca atg aag aga ggg ctc tgc tgt gtg ctg ctg ctg tgt gga Met Asp Ala Met Lys Arg Gly Leu Cys Cys Val Leu Leu Leu Cys Gly 1 5 10 15	48
gca gtc ttc gtt tgc ccc agc gag atc tcc att gtg tgg gcc tcc agg Ala Val Phe Val Ser Pro Ser Glu Ile Ser Ile Val Trp Ala Ser Arg 20 25 30	96
gag ctg gag agg ttt gct gtg aac cct ggc ctg ctg gag acc tct gag Glu Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser Glu 35 40 45	144
ggg tgc agg cag atc ctg ggc cag ctc cag ccc tcc ctg caa aca ggc Gly Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly 50 55 60	192
tct gag gag ctg agg tcc ctg tac aac aca gtg gct acc ctg tac tgt Ser Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr Cys 65 70 75 80	240
gtg cac cag aag att gat gtg aag gac acc aag gag gcc ctg gag aag Val His Gln Lys Ile Asp Val Lys Asp Thr Lys Glu Ala Leu Glu Lys 85 90 95	288
att gag gag gag cag aac aag tcc aag aag aag gcc cag cag gct gct Ile Glu Glu Glu Gln Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala Ala 100 105 110	336
gct ggc aca ggc aac tcc agc cag gtg tcc cag aac tac ccc att gtg Ala Gly Thr Gly Asn Ser Ser Gln Val Ser Gln Asn Tyr Pro Ile Val 115 120 125	384
cag aac ctc cag ggc cag atg gtg cac cag gcc atc tcc ccc cgg acc Gln Asn Leu Gln Gly Gln Met Val His Gln Ala Ile Ser Pro Arg Thr 130 135 140	432
ctg aat gcc tgg gtg aag gtg gtg gag gag aag gcc ttc tcc cct gag Leu Asn Ala Trp Val Lys Val Val Glu Glu Lys Ala Phe Ser Pro Glu 145 150 155 160	480
gtg atc ccc atg ttc tct gcc ctg tct gag ggt gcc acc ccc cag gac Val Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr Pro Gln Asp 165 170 175	528
ctg aac acc atg ctg aac aca gtg ggg ggc cat cag gct gcc atg cag Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met Gln 180 185 190	576
atg ctg aag gag acc atc aat gag gag gct gct gag tgg gac agg ctg Met Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg Leu 195 200 205	624
cat cct gtg cac gct ggc ccc att gcc ccc ggc cag atg agg gag ccc His Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu Pro 210 215 220	672
agg ggc tct gac att gct ggc acc acc tcc acc ctc cag gag cag att Arg Gly Ser Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln Ile 225 230 235 240	720
ggc tgg atg acc aac aac ccc ccc atc cct gtg ggg gaa atc tac aag Gly Trp Met Thr Asn Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys 245 250 255	768

Figure 30A'

agg tgg atc atc ctg ggc ctg aac aag att gtg agg atg tac tcc ccc Arg Trp Ile Ile Leu Gly Leu Asn Lys Ile Val Arg Met Tyr Ser Pro 260 265 270	816
acc tcc atc ctg gac atc agg cag ggc ccc aag gag ccc ttc agg gac Thr Ser Ile Leu Asp Ile Arg Gln Gly Pro Lys Glu Pro Phe Arg Asp 275 280 285	864
tat gtg gac agg ttc tac aag acc ctg agg gct gag cag gcc tcc cag Tyr Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala Glu Gln Ala Ser Gln 290 295 300	912
gag gtg aag aac tgg atg aca gag acc ctg ctg gtg cag aat gcc aac Glu Val Lys Asn Trp Met Thr Glu Thr Leu Leu Val Gln Asn Ala Asn 305 310 315	960
cct gac tgc aag acc atc ctg aag gcc ctg ggc cct gct gcc acc ctg Pro Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr Leu 325 330 335	1008
gag gag atg atg aca gcc tgc cag ggg gtg ggg ggc cct ggt cac aag Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His Lys 340 345 350	1056
gcc agg gtg ctg gct gag gcc atg tcc cag gtg acc aac tcc gcc acc Ala Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Ser Ala Thr 355 360 365	1104
atc atg atg cag agg ggc aac ttc agg aac cag agg aag aca gtg aag Ile Met Met Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Thr Val Lys 370 375 380	1152
tgc ttc aac tgt ggc aag gtg ggc cac att gcc aag aac tgt agg gcc Cys Phe Asn Cys Gly Lys Val Gly His Ile Ala Lys Asn Cys Arg Ala 385 390 395 400	1200
ccc agg aag aag ggc tgc tgg aag tgt ggc aag gag ggc cac cag atg Pro Arg Lys Lys Gly Cys Trp Lys Cys Gly Lys Glu Gly His Gln Met 405 410 415	1248
aag gac tgc aat gag agg cag gcc aac ttc ctg ggc aaa atc tgg ccc Lys Asp Cys Asn Glu Arg Gln Ala Asn Phe Leu Gly Lys Ile Trp Pro 420 425 430	1296
tcc cac aag ggc agg cct ggc aac ttc ctc cag tcc agg cct gag ccc Ser His Lys Gly Arg Pro Gly Asn Phe Leu Gln Ser Arg Pro Glu Pro 435 440 445	1344
aca gcc cct ccc gag gag tcc ttc agg ttt ggg gag gag aag acc acc Thr Ala Pro Pro Glu Glu Ser Phe Arg Phe Gly Glu Glu Lys Thr Thr 450 455 460	1392
ccc agc cag aag cag gag ccc att gac aag gag ctg tac ccc ctg gcc Pro Ser Gln Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu Ala 465 470 475 480	1440
tcc ctg agg tcc ctg ttt ggc aac gac ccc tcc tcc cag taa (SID NO:36) 1482 Ser Leu Arg Ser Leu Phe Gly Asn Asp Pro Ser Ser Gln * (SID NO:37) 485 490	

Figure 30 B

Figure 31

IFN- $\gamma$  Secretion against Gag 20-aa pool from CD3<sup>+</sup> T cells of Monkey PBMCs

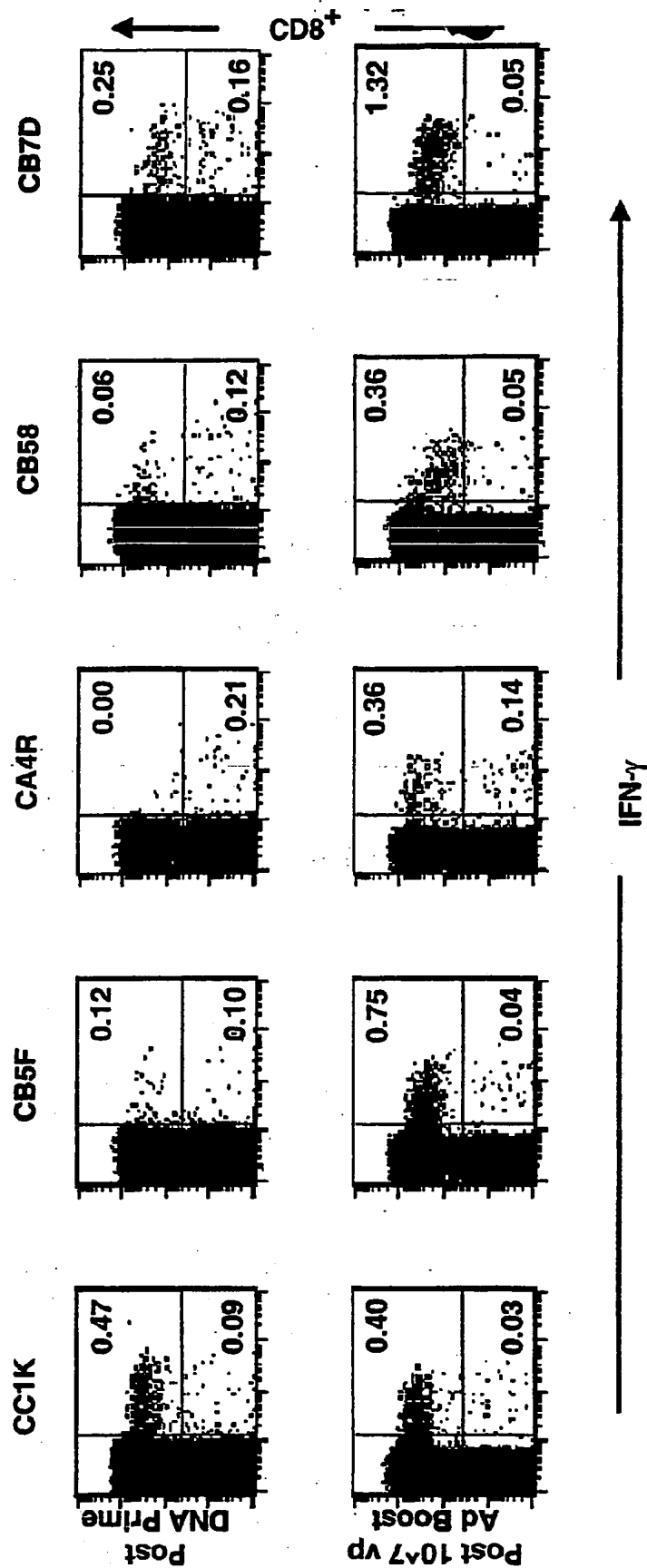


FIGURE 32

# **Comparison of Single-Modality Adenovirus Immunization with DNA+Adjuvant Prime/Adenovirus Boost**

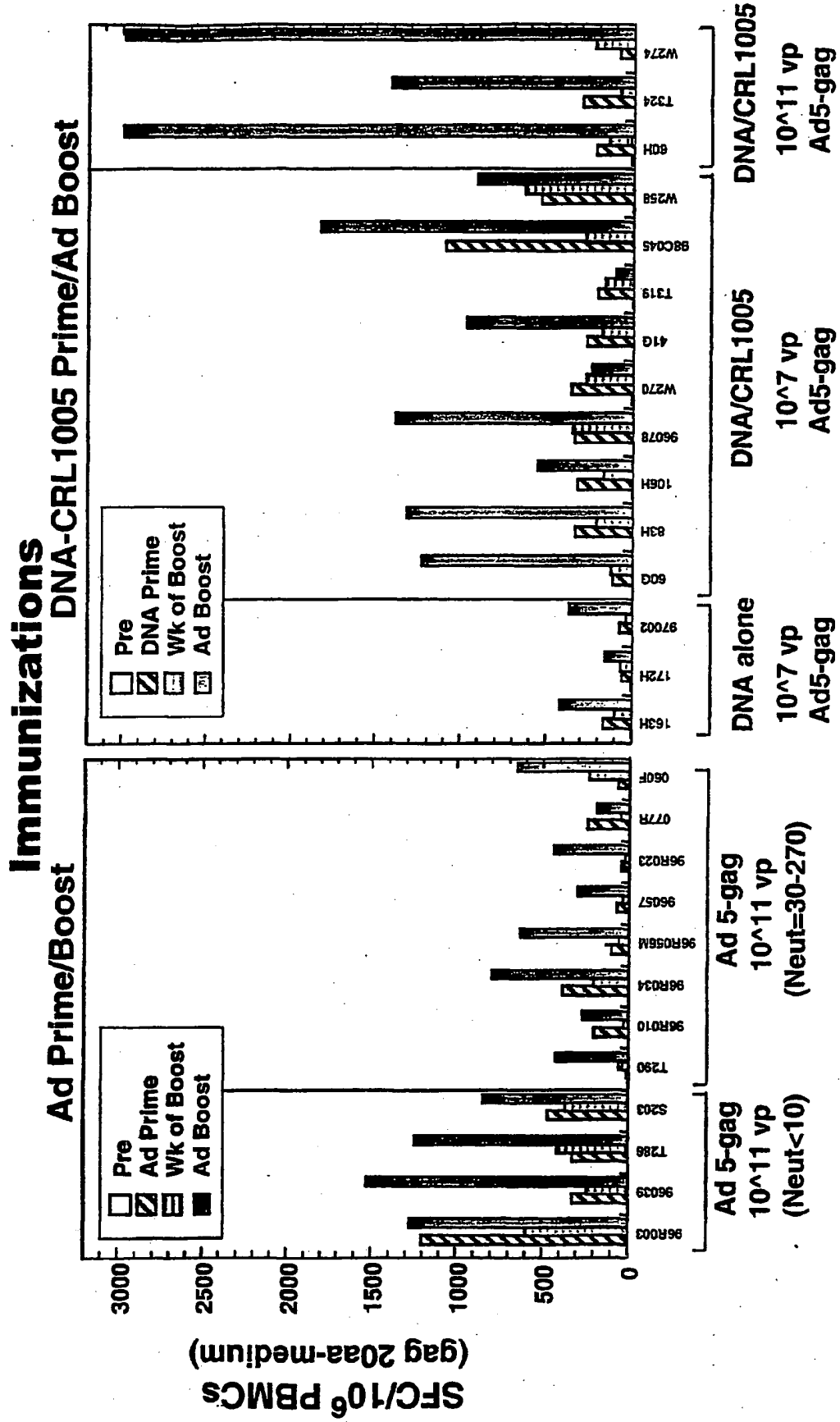


FIGURE 33A

ATGGGTGCTA GGGCTTCTGT GCTGTCTGGT GGTGAGCTGG ACAAGTGGGA GAAGATCAGG  
 CTGAGGCCTG GTGGCAAGAA GAAGTACAAG CTAAAGCACA TTGTGTGGGC CTCCAGGGAG  
 CTGGAGAGGT TTGCTGTGAA CCCTGGCCTG CTGGAGACCT CTGAGGGGTG CAGGCAGATC  
 CTGGGCCAGC TCCAGCCCTC CCTGCAAACA GGCTCTGAGG AGCTGAGGTC CCTGTACAAC  
 ACAGTGGCTA CCCTGTACTG TGTGCACCAG AAGATTGATG TGAAGGACAC CAAGGAGGCC  
 CTGGAGAAGA TTGAGGAGGA GCAGAACAAG TCCAAGAAGA AGGCCAGCA GGCTGCTGCT  
 GGCACAGGCA ACTCCAGCCA GGTGTCCAG AACTACCCCA TTGTGCAGAA CCTCCAGGGC  
 CAGATGGTGC ACCAGGCCAT CCCCCCCGG ACCCTGAATG CCTGGGTGAA GGTGGTGGAG  
 GAGAAGGCCT TCTCCCTGA GGTGATCCCC ATGTTCTCTG CCCTGTCTGA GGGTGCCACC  
 CCCCAGGACC TGAACACCAT GCTGAACACA GTGGGGGGCC ATCAGGCTGC CATGCAGATG  
 CTGAAGGAGA CCATCAATGA GGAGGCTGCT GAGTGGGACA GGCTGCATCC TGTGCACGCT  
 GGCCCCATTG CCCCCGGCCA GATGAGGGAG CCCAGGGGCT CTGACATTGC TGGCACCACC  
 TCCACCCTCC AGGAGCAGAT TGGCTGGATG ACCAACAACC CCCCATCCC TGTGGGGGAA  
 ATCTACAAGA GGTGGATCAT CCTGGGCCTG AACAAGATTG TGAGGATGTA CTCCCCACC  
 TCCATCCTGG ACATCAGGCA GGGCCCCAAG GAGCCCTTCA GGGACTATGT GGACAGGTTT  
 TACAAGACCC TGAGGGCTGA GCAGGCCTCC CAGGAGGTGA AGAACTGGAT GACAGAGACC  
 CTGCTGGTGC AGAATGCCAA CCCTGACTGC AAGACCATCC TGAAGGCCCT GGGCCCTGCT  
 GCCACCCTGG AGGAGATGAT GACAGCCTGC CAGGGGGTGG GGGGCCCTGG TCACAAGGCC  
 AGGGTGCTGG CTGAGGCCAT GTCCAGGTG ACCAACTCCG CCACCATCAT GATGCAGAGG  
 GGCAACTTCA GGAACCAGAG GAAGACAGTG AAGTGCTTCA ACTGTGGCAA GGTGGGCCAC  
 ATTGCCAAGA ACTGTAGGGC CCCAGGAAG AAGGGCTGCT GGAAGTGTTG CAAGGAGGGC  
 CACCAGATGA AGGACTGCAA TGAGAGGCAG GCCAACTTCC TGGGCAAAT CTGGCCCTCC  
 CACAAGGGCA GGCCTGGCAA CTTCTCCAG TCCAGGCCTG AGCCACAGC CCCTCCCGAG  
 GAGTCCTTCA GGTTTGGGGA GGAGAAGACC ACCCCCAGCC AGAAGCAGGA GCCCATTGAC  
 AAGGAGCTGT ACCCCCTGGC CTCCTGAGG TCCCTGTTG GCAACGACCC CTCCTCCAG  
 ATGGCTCCA TCTCCCCAT TGAGACTGTG CCTGTGAAGC TGAAGCCTGG CATGGATGGC  
 CCCAAGGTGA AGCAGTGGCC CCTGACTGAG GAGAAGATCA AGGCCCTGGT GGAAATCTGC  
 ACTGAGATGG AGAAGGAGGG CAAAATCTCC AAGATTGGCC CCGAGAACCC CTACAACACC  
 CCTGTGTTG CCATCAAGAA GAAGGACTCC ACCAAGTGA GGAAGCTGGT GGACTTCAGG  
 GAGCTGAACA AGAGGACCCA GGACTTCTGG GAGGTGCAGC TGGGCATCCC CCACCCCGCT  
 GGCCTGAAGA AGAAGAAGTC TGTGACTGTG CTGGCTGTGG GGGATGCCTA CTTCTCTGTG  
 CCCCTGGATG AGGACTTCAG GAAGTACACT GCCTTCACCA TCCCCTCCAT CAACAATGAG  
 ACCCTGGCA TCAGGTACCA GTACAATGTG CTGCCCAGG GCTGGAAGGG CTCCCCTGCC  
 ATCTTCCAGT CCTCCATGAC CAAGATCCTG GAGCCCTTCA GGAAGCAGAA CCCTGACATT  
 GTGATCTACC AGTACATGGC TGCCCTGTAT GTGGGCTCTG ACCTGGAGAT TGGGCAGCAC  
 AGGACCAAGA TTGAGGAGCT GAGGCAGCAC CTGCTGAGGT GGGGCTGAC CAGCCCTGAC  
 AAGAAGCACC AGAAGGAGCC CCCCTTCTG TGGATGGGCT ATGAGCTGCA CCCCACAAG  
 TGGACTGTGC AGCCCATTTG GCTGCCTGAG AAGGACTCCT GGACTGTGAA TGACATCCAG  
 AAGCTGGTGG GCAAGCTGAA CTGGGCTCC CAAATCTACC CTGGCATCAA GGTGAGGCAG  
 CTGTGCAAGC TGCTGAGGGG CACCAAGGCC CTGACTGAGG TGATCCCCCT GACTGAGGAG  
 GCTGAGCTGG AGCTGGCTGA GAACAGGGAG ATCCTGAAGG AGCCTGTGCA TGGGGTGTAC

FIGURE 33B

TATGACCCCT CCAAGGACCT GATTGCTGAG ATCCAGAAGC AGGGCCAGGG CCAGTGGACC  
TACCAAATCT ACCAGGAGCC CTTCAAGAAC CTGAAGACTG GCAAGTATGC CAGGATGAGG  
GGGGCCACACA CCAATGATGT GAAGCAGCTG ACTGAGGCTG TGCAGAAGAT CACCACTGAG  
TCCATTGTGA TCTGGGGCAA GACCCCAAG TTCAAGCTGC CCATCCAGAA GGAGACCTGG  
GAGACCTGGT GGA CTGAGTA CTGGCAGGCC ACCTGGATCC CTGAGTGGGA GTTTGTGAAC  
ACCCCCCCCC TGGTGAAGCT GTGGTACCAG CTGGAGAAGG AGCCCATTGT GGGGGCTGAG  
ACCTTCTATG TGGCTGGGGC TGCCAACAGG GAGACCAAGC TGGGCAAGGC TGGCTATGTG  
ACCAACAGGG GCAGGCAGAA GGTGGTGACC CTGACTGACA CCACCAACCA GAAGACTGCC  
CTCCAGGCCA TCTACCTGGC CCTCCAGGAC TCTGGCCTGG AGGTGAACAT TGTGACTGCC  
TCCCAGTATG CCCTGGGCAT CATCCAGGCC CAGCCTGATC AGTCTGAGTC TGAGCTGGTG  
AACCAGATCA TTGAGCAGCT GATCAAGAAG GAGAAGGTGT ACCTGGCCTG GGTGCCTGCC  
CACAAGGGCA TTGGGGGCAA TGAGCAGGTG GACAAGCTGG TGTCTGCTGG CATCAGGAAG  
GTGCTGTTCC TGGATGGCAT TGACAAGGCC CAGGATGAGC ATGAGAAGTA CCACTCCAAC  
TGGAGGGCTA TGGCCTCTGA CTTCAACCTG CCCCCTGTGG TGGCTAAGGA GATTGTGGCC  
TCCTGTGACA AGTGCCAGCT GAAGGGGGAG GCCATGCATG GGCAGGTGGA CTGCTCCCCT  
GGCATCTGGC AGCTGGCCTG CACCCACCTG GAGGGCAAGG TGATCCTGGT GGCTGTGCAT  
GTGGCCTCCG GCTACATTGA GGCTGAGGTG ATCCCTGCTG AGACAGGCCA GGAGACTGCC  
TACTTCCTGC TGAAGCTGGC TGGCAGGTGG CCTGTGAAGA CCATCCACAC TGCCAATGGC  
TCCAACCTCA CTGGGGCCAC AGTGAGGGCT GCCTGCTGGT GGGCTGGCAT CAAGCAGGAG  
TTTGGCATCC CCTACAACCC CCAGTCCCAG GGGGTGGTGG CCTCCATGAA CAAGGAGCTG  
AAGAAGATCA TTGGGCAGGT GAGGGACCAG GCTGAGCACC TGAAGACAGC TGTGCAGATG  
GCTGTGTTCA TCCACAACCT CAAGAGGAAG GGGGGCATCG GGGGCTACTC CGCTGGGGAG  
AGGATTGTGG ACATCATTGC CACAGACATC CAGACCAAGG AGCTCCAGAA GCAGATCACC  
AAGATCCAGA ACTTCAGGGT GTACTACAGG GACTCCAGGA ACCCCCTGTG GAAGGGCCCT  
GCCAAGCTGC TGTGGAAGGG GGAGGGGGCT GTGGTGATCC AGGACAACCTC TGACATCAAG  
GTGGTGCCCA GGAGGAAGGC CAAGATCATC AGGGACTATG GCAAGCAGAT GGCTGGGGAT  
GACTGTGTGG CCTCCAGGCA GGATGAGGAC TAA

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FIGURE 34A

Met Gly Ala Arg Ala Ser Val Leu Ser Gly Gly Glu Leu Asp Lys Trp Glu Lys  
 Ile Arg Leu Arg Pro Gly Gly Lys Lys Lys Tyr Lys Leu Lys His Ile Val Trp  
 Ala Ser Arg Glu Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser  
 Glu Gly Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly Ser  
 Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr Cys Val His Gln  
 Lys Ile Asp Val Lys Asp Thr Lys Glu Ala Leu Glu Lys Ile Glu Glu Glu Gln  
 Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala Ala Ala Gly Thr Gly Asn Ser Ser  
 Gln Val Ser Gln Asn Tyr Pro Ile Val Gln Asn Leu Gln Gly Gln Met Val His  
 Gln Ala Ile Ser Pro Arg Thr Leu Asn Ala Trp Val Lys Val Val Glu Glu Lys  
 Ala Phe Ser Pro Glu Val Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr  
 Pro Gln Asp Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met  
 Gln Met Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg Leu His  
 Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu Pro Arg Gly Ser  
 Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln Ile Gly Trp Met Thr Asn  
 Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys Arg Trp Ile Ile Leu Gly Leu  
 Asn Lys Ile Val Arg Met Tyr Ser Pro Thr Ser Ile Leu Asp Ile Arg Gln Gly  
 Pro Lys Glu Pro Phe Arg Asp Tyr Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala  
 Glu Gln Ala Ser Gln Glu Val Lys Asn Trp Met Thr Glu Thr Leu Leu Val Gln  
 Asn Ala Asn Pro Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr  
 Leu Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His Lys Ala  
 Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Ser Ala Thr Ile Met Met  
 Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Thr Val Lys Cys Phe Asn Cys Gly  
 Lys Val Gly His Ile Ala Lys Asn Cys Arg Ala Pro Arg Lys Lys Gly Cys Trp  
 Lys Cys Gly Lys Glu Gly His Gln Met Lys Asp Cys Asn Glu Arg Gln Ala Asn  
 Phe Leu Gly Lys Ile Trp Pro Ser His Lys Gly Arg Pro Gly Asn Phe Leu Gln  
 Ser Arg Pro Glu Pro Thr Ala Pro Pro Glu Glu Ser Phe Arg Phe Gly Glu Glu  
 Lys Thr Thr Pro Ser Gln Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu  
 Ala Ser Leu Arg Ser Leu Phe Gly Asn Asp Pro Ser Ser Gln Met Ala Pro Ile  
 Ser Pro Ile Glu Thr Val Pro Val Lys Leu Lys Pro Gly Met Asp Gly Pro Lys  
 Val Lys Gln Trp Pro Leu Thr Glu Glu Lys Ile Lys Ala Leu Val Glu Ile Cys  
 Thr Glu Met Glu Lys Glu Gly Lys Ile Ser Lys Ile Gly Pro Glu Asn Pro Tyr  
 Asn Thr Pro Val Phe Ala Ile Lys Lys Lys Asp Ser Thr Lys Trp Arg Lys Leu  
 Val Asp Phe Arg Glu Leu Asn Lys Arg Thr Gln Asp Phe Trp Glu Val Gln Leu  
 Gly Ile Pro His Pro Ala Gly Leu Lys Lys Lys Lys Ser Val Thr Val Leu Ala  
 Val Gly Asp Ala Tyr Phe Ser Val Pro Leu Asp Glu Asp Phe Arg Lys Tyr Thr  
 Ala Phe Thr Ile Pro Ser Ile Asn Asn Glu Thr Pro Gly Ile Arg Tyr Gln Tyr  
 Asn Val Leu Pro Gln Gly Trp Lys Gly Ser Pro Ala Ile Phe Gln Ser Ser Met  
 Thr Lys Ile Leu Glu Pro Phe Arg Lys Gln Asn Pro Asp Ile Val Ile Tyr Gln  
 Tyr Met Ala Ala Leu Tyr Val Gly Ser Asp Leu Glu Ile Gly Gln His Arg Thr  
 Lys Ile Glu Glu Leu Arg Gln His Leu Leu Arg Trp Gly Leu Thr Thr Pro Asp  
 Lys Lys His Gln Lys Glu Pro Pro Phe Leu Trp Met Gly Tyr Glu Leu His Pro

FIGURE 34B

Asp Lys Trp Thr Val Gln Pro Ile Val Leu Pro Glu Lys Asp Ser Trp Thr Val  
Asn Asp Ile Gln Lys Leu Val Gly Lys Leu Asn Trp Ala Ser Gln Ile Tyr Pro  
Gly Ile Lys Val Arg Gln Leu Cys Lys Leu Leu Arg Gly Thr Lys Ala Leu Thr  
Glu Val Ile Pro Leu Thr Glu Glu Ala Glu Leu Glu Leu Ala Glu Asn Arg Glu  
Ile Leu Lys Glu Pro Val His Gly Val Tyr Tyr Asp Pro Ser Lys Asp Leu Ile  
Ala Glu Ile Gln Lys Gln Gly Gln Gly Gln Trp Thr Tyr Gln Ile Tyr Gln Glu  
Pro Phe Lys Asn Leu Lys Thr Gly Lys Tyr Ala Arg Met Arg Gly Ala His Thr  
Asn Asp Val Lys Gln Leu Thr Glu Ala Val Gln Lys Ile Thr Thr Glu Ser Ile  
Val Ile Trp Gly Lys Thr Pro Lys Phe Lys Leu Pro Ile Gln Lys Glu Thr Trp  
Glu Thr Trp Trp Thr Glu Tyr Trp Gln Ala Thr Trp Ile Pro Glu Trp Glu Phe  
Val Asn Thr Pro Pro Leu Val Lys Leu Trp Tyr Gln Leu Glu Lys Glu Pro Ile  
Val Gly Ala Glu Thr Phe Tyr Val Ala Gly Ala Ala Asn Arg Glu Thr Lys Leu  
Gly Lys Ala Gly Tyr Val Thr Asn Arg Gly Arg Gln Lys Val Val Thr Leu Thr  
Asp Thr Thr Asn Gln Lys Thr Ala Leu Gln Ala Ile Tyr Leu Ala Leu Gln Asp  
Ser Gly Leu Glu Val Asn Ile Val Thr Ala Ser Gln Tyr Ala Leu Gly Ile Ile  
Gln Ala Gln Pro Asp Gln Ser Glu Ser Glu Leu Val Asn Gln Ile Ile Glu Gln  
Leu Ile Lys Lys Glu Lys Val Tyr Leu Ala Trp Val Pro Ala His Lys Gly Ile  
Gly Gly Asn Glu Gln Val Asp Lys Leu Val Ser Ala Gly Ile Arg Lys Val Leu  
Phe Leu Asp Gly Ile Asp Lys Ala Gln Asp Glu His Glu Lys Tyr His Ser Asn  
Trp Arg Ala Met Ala Ser Asp Phe Asn Leu Pro Pro Val Val Ala Lys Glu Ile  
Val Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu Ala Met His Gly Gln Val  
Asp Cys Ser Pro Gly Ile Trp Gln Leu Ala Cys Thr His Leu Glu Gly Lys Val  
Ile Leu Val Ala Val His Val Ala Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro  
Ala Glu Thr Gly Gln Glu Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp  
Pro Val Lys Thr Ile His Thr Ala Asn Gly Ser Asn Phe Thr Gly Ala Thr Val  
Arg Ala Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn  
Pro Gln Ser Gln Gly Val Val Ala Ser Met Asn Lys Glu Leu Lys Lys Ile Ile  
Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val Gln Met Ala Val  
Phe Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly Gly Tyr Ser Ala Gly Glu  
Arg Ile Val Asp Ile Ile Ala Thr Asp Ile Gln Thr Lys Glu Leu Gln Lys Gln  
Ile Thr Lys Ile Gln Asn Phe Arg Val Tyr Tyr Arg Asp Ser Arg Asn Pro Leu  
Trp Lys Gly Pro Ala Lys Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln  
Asp Asn Ser Asp Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp  
Tyr Gly Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp  
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